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CARDIAC SIGNS IN RHEUMATIC INFECTION OF CHILDHOOD

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In a previous paper [1] a statistical analysis was presented of data for a group of patients with rheumatic infection who had been treated in the Children's Hospital, Philadelphia, during the period from 1922 to 1932 inclusive. A further follow-up study was made in 1939 of the children whose primary manifestation of rheumatic infection had occurred during the period between 1922 and 1936. Data for all children for whom a diagnosis of rheumatic infection was made were included, irrespective of the presence or absence of clinically recognizable heart disease. Details concerning the composition of this group have been reported elsewhere.[2]

As a result of the survey the course of 553 children (94.8 per cent of the total group) was known for a minimum period of three years and an average period of nine and six-tenths years after the primary manifestation. The severity of the disease was greatest in the case of the children first taken ill with acute carditis, and the outcome was most favorable for those whose initial manifestation was chorea (table 1: chart). The death rate was higher during the first year after onset than during any single year thereafter. The percentage incidence of deaths was greater among boys (27) than among girls (23) and higher among the Negro (32) than among the white children (23).

At the time of last observation a diagnosis of valvular heart disease was made for 64 per cent of the children. Sixty-one per cent of the group were leading a normal existence. Five per cent were either cardiac invalids or suffering from recurrences of rheumatic infection. Twenty-four per cent had died of heart disease. A comparison of these results with those of other observers is outlined in table 2.

From the Department of Pediatrics, University of Pennsylvania School of Medicine, and the Children's Hospital.

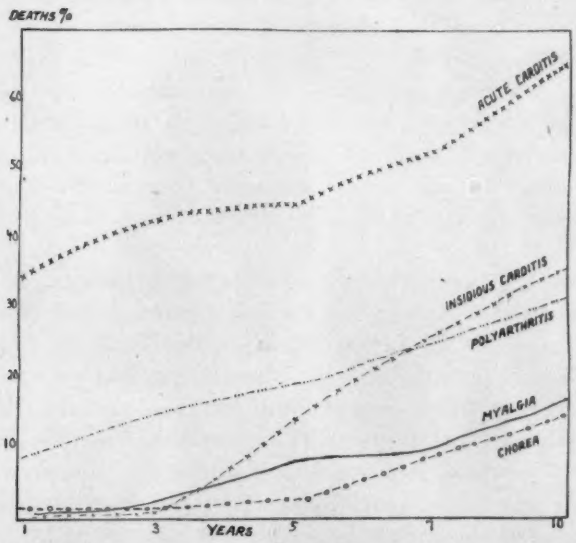
1. Ash, R.: Prognosis of Rheumatic Infection in Childhood: A Statistical Study, Am. J. Dis. Child. **52**:280 (Aug.) 1936.

2. Ash, R.: Rheumatic Infection in Childhood: Influence of Type of Onset and Calendar Year of Onset, Am. Heart J. **22**:439 (Oct.) 1941.

In the present paper an analysis of the physical signs of heart disease noted during the period of observation is presented. A preliminary report has been published elsewhere.[3] The criteria for the diagnosis of

TABLE 1.—*Relation of Type of Onset and Outcome in Cases of Rheumatic Infection in Childhood*

Type of Onset	Number of Patients	Average Age, Years	Incidence of Valvular Heart Disease, Percentage	Deaths, Percentage
Acute carditis	47	5.7	100	29.8
Polyarthritis	314	6.6	59	9.6
Myalgia; joint pains	53	7.5	47	0.0
Chorea	116	8.0	22	2.6
Insidious carditis	48	7.0	100	0.0
Total	578	6.9	62	7.9



Influence of type of onset on mortality rate during the first ten years of rheumatic infection.

heart disease were those advocated by the American Heart Association.[4] For the detection of cardiac enlargement use was made only of the position of the apex beat as determined by palpation, aided by the teleroentgenogram. No application was made of the angle of clearance test described by Wilson.[5]

3. Ash, R.: The Evolution of Rheumatic Heart Disease in Childhood, Pennsylvania M. J. **44**:484, 1941.

4. Criteria for the Diagnosis and Classification of Heart Disease, New York, American Heart Association, 1932.

5. Wilson, M. G.: Clinical Radioscopic Studies of the Heart in Children, Am. J. Dis. Child. **47**:750 (April) 1934.

The condition of the 19 per cent of the group who had had neither cardiac enlargement nor murmurs during the initial illness was classified as potential heart disease. In an additional 19 per cent the heart had remained within normal limits of size but systolic murmurs of the type usually considered accidental or functional were audible. Such children were classified as having potential and possible heart disease. The appearance of some degree of cardiac enlargement accompanied by a systolic blow maximum at the apex, with or without an associated mid-diastolic blow, was accepted as an indication of mitral disease. A diastolic blow to the left of the sternum was interpreted as the result of involvement of the aortic valve. A diagnosis of valvular disease was made for 62 per cent of the patients after recovery from the first manifestation of rheumatic infection.

TABLE 2.—*Outcome in Cases of Rheumatic Infection in Childhood*

Author	Number of Patients Traced	Average Age at Onset, Years	Duration, Years	Incidence of Valvular Heart Disease, Percentage	Percentage of Patients	
					Dead	Leading Normal Existence
Findlay [10a] (1931).....	669	±7	2 to 22	78.9	23.1	
	561	±7	2 to 12	67.4	19.6	
Schlesinger [17b] (1938).....	1,000	±7	1 to 10	73.8	12.3	81.7
Jones, T. D.: J. Pediat. **14**: 395, 1939	1,000	8.0	Over 10	66.9	24.0	59.7
Wilson, M. G.: Rheumatic Fever, New York, Commonwealth Fund Division of Publications, 1940, chap. 6	717	6±.1	Average, 8	90.5*	16.3	66.6
Ash (present series) (1941).....	553	6.9	3 to 17 Average, 9.6	64.2	24.0	61.1

* Cardiac involvement was diagnosed not only in accordance with the criteria used for the present study but in the presence of cardiac enlargement alone, as determined by roentgen examination in frontal and oblique views. "Minimal cardiac damage" was present in one third of the cases.

In the case of the patients with so-called potential and possible heart disease it is probable that pathologic examination of the heart during the active phase of infection would have disclosed changes of rheumatic origin. Bearing on this point is the case mentioned by Swift.[6] In the heart of a fever-free patient who succumbed to an anesthetic on the nineteenth day after the onset of an apparently mild monocyclic course there were found edema and cellular infiltration of the aortic valve together with one small verruca. Early mild interstitial inflammation of the mitral valve and splitting of the elastica and early mural thrombus formation of the coronary artery were also present.

Probably the most marked difference between children with enlarged hearts associated with murmurs suggesting valvular damage and those with absence of or minimal signs lies in the degree of myocardial involvement and resultant dilatation, which is dependent on the severity of

6. Swift, H. F.: Rheumatic Heart Disease: Pathogenesis and Etiology in Their Relation to Therapy and Prophylaxis, Medicine **19**:417, 1940.

the infection and the resistance of the patient. The course of children with potential or possible heart disease proved to be more favorable not only at onset but throughout the succeeding ten years of infection (tables 3 and 4). In spite of recurrences the death rate remained relatively low.

TABLE 3.—*Outcome in Cases of Rheumatic Infection in Childhood with Acute Carditis at Onset**

			Deaths		Survivors				
Number of Patients Traced	Percentage of Total Group Traced	Percentage Incidence of Rheumatic Heart Disease	From Rheumatic Heart Disease, per Cent	From Other Causes, Number	Number	Percentage with Rheumatic Heart Disease	Number with Possible Heart Disease	Number with Potential Heart Disease	Survival Period, Years
234	96.3	90.1	19.0	2	187	87.7	6	17	1
229	94.2	89.0	27.5	2	164	85.3	6	18	3
205	94.5	88.3	30.7	4	138	85.5	9	15	5
171	91.9	87.7	35.0	5	106	79.2	9	13	7
121	86.9	90.9	45.4	4	62	85.4	1	8	10

* All cases in which an initial diagnosis of acute carditis was made, whether primary or associated with polyarthritis or chorea, are included.

TABLE 4.—*Outcome in Cases of Rheumatic Infection in Childhood with Potential or Possible Heart Disease at Onset*

			Polyarthritis						
			Deaths		Survivors				
Number of Patients Traced	Percentage of Total Group Traced	Percentage with Rheumatic Heart Disease	From Rheumatic Heart Disease, Percentage	From Other Causes, Number	Number	Percentage with Rheumatic Heart Disease	Number with Possible Heart Disease	Number with Potential Heart Disease	Survival Period, Years
90	94.7	5.5	...	1	89	4.5	28	57	1
90	94.7	15.5	...	1	89	13.5	23	54	3
75	95.0	21.3	...	1	74	20.2	13	46	5
56	91.8	25.0	3.5	..	54	22.2	8	34	7
34	91.6	23.5	2.9	..	33	21.2	5	21	10
			Chorea						
78	97.5	3.8	1.3	..	77	2.6	8	67	1
75	92.6	10.6	1.3	..	74	9.5	10	57	3
69	92.0	21.7	1.4	3	65	21.5	6	45	5
53	88.3	26.4	5.6	2	48	23.0	7	30	7
32	78.0	31.2	9.4	1	28	25.0	1	20	10

REGRESSION OF CARDIAC SIGNS

Subsequent disappearance of physical signs of heart disease has been reported by various observers.[7] In the present series regression of

7. (*a*) Coombs, C.: Rheumatic Heart Disease, New York, William Wood & Company, 1924. (*b*) Ehler, A.: Subsidence of Heart Signs in Rheumatic Fever, Yale J. Biol. & Med. **5**:509, 1933. (*c*) Wilson, M. G.: Diagnosis of Heart Disease in Children: Regression of Physical Signs, J. A. M. A. **110**:501 (Feb. 12) 1938. (*d*) Bland, E. F.; Jones, T. D., and White, P. D.: Disappearance of Physical

cardiac signs occurred in approximately 10 per cent of the 340 cases in which the diagnosis of heart disease was made after recovery from the initial illness. In 6 cases both middiastolic and systolic blows disappeared. In the remainder only systolic murmurs had been present. In approximately half the cases disappearance of the signs occurred within a year; in the remainder the process was more gradual, extending over a period of years. Such regression of cardiac signs may not necessarily indicate the disappearance of all anatomic trace of the rheumatic infection. Wilson [7c] has pointed out that in some cases the heart sounds have returned to normal and no enlargement of the heart can be demonstrated by measurement of the frontal plane of the cardiac silhouette but oblique views may yet demonstrate enlargement of the left auricle or ventricle.

In the majority of cases such anatomic changes as persist, however, are probably unimportant in degree. In a case reported by Bland, Jones and White [7d] (that of a 20 year old woman who died unexpectedly in a dentist's chair) postmortem examination revealed slight but definite scarring of the mitral cusps of sufficient degree to warrant the pathologic diagnosis, on macroscopic examination, of healed rheumatic endocarditis. There remained, however, no important deformity, and there was no detectable scarring of the aortic cusps. The weight of the heart was within the normal range. During her initial illness, at the age of 13 years, this patient's heart had been enlarged. Apical systolic and diastolic murmurs were audible, together with a soft diastolic murmur along the left sternal border. These had gradually disappeared, so that for two years prior to death no murmur had been heard.

A 19 year old woman in the present series died of pyelonephritis shortly after being delivered of her first child. She had suffered from rheumatic fever at the ages of 9 and 14 years. During her initial illness there had been some cardiac enlargement, with a distinct systolic murmur transmitted out into the left axilla. When seen at the Children's Hospital four months before her death, she was stocky and somewhat obese, with an apex beat 8.5 cm. from the midsternal line. In the recumbent position a short, soft, systolic blow, which was not transmitted, was audible to the right of the apex. At necropsy the weight of the heart was 350 Gm. A little wrinkling of the left auricular endocardium, slight opacity of certain chordae tendineae and very slight thickening of the free edges of the mitral valve were the residual evidences of the original rheumatic infection. Functionally the mitral valve seemed adequate.

The absence of anatomic changes in a child with potential heart disease is illustrated by the case of a boy in the present series who

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Signs of Rheumatic Heart Disease, ibid. **107**:569 (Aug. 22) 1936. (*e*) Brown, M. G., and Wolff, L.: Recovery from Acute Rheumatic Fever Without Permanent Cardiac Damage, New England J. Med. **223**:242, 1940.

suffered from chorea at the age of 10 years and again at 12 years and who died at the age of 14, of nephrosis and hemolytic septicemia. At necropsy there were no residual signs of rheumatic infection within the heart.

PROGRESSION OF CARDIAC SIGNS

The delayed appearance of heart disease after recovery from rheumatic fever has been commented on previously.[8] In 39, or 19 per cent, of the 209 cases in the present series in which an initial diagnosis of potential or possible heart disease was made definite cardiac lesions subsequently developed. The incidence ranged from 5 per cent at the end of one year to approximately 20 per cent at the end of five years and 25 per cent at the end of ten years among the patients who had recovered from an initial attack of polyarthritis without obvious cardiac damage. In the cases in which simple chorea was present at onset valvular lesions had developed in 4 per cent at the end of one year, in 21 per cent at the end of five years and in 31 per cent at the end of ten years (table 4). The subsequent signs of valvular deformity made their appearance in 32 (82 per cent) of the cases in association with acute recrudescences of rheumatism. On the other hand, in the seeming absence of infection and after a prolonged latent period the murmur of mitral stenosis became audible in 5 cases and that of aortic insufficiency in 1.

In Boston[8c] of 314 cases of potential heart disease in which the patient was followed for a period of ten years or more signs of permanent valvular deformity appeared in 79 (25 per cent). Recrudescences of rheumatic fever or chorea were associated with the appearance of such valvular damage in approximately two thirds of these 79 cases. In the remaining one third signs of valvular disease appeared insidiously, without other clinical evidence of coexisting activity of the rheumatic infection. Boone and Levine,[8b] dealing with an older group of patients who were first seen at an average age of 14 years, found that of 166 patients with potential heart disease, signs of valvular deformity subsequently developed in 4.8 per cent over an average period of observation of nine and six-tenths years.

MITRAL VALVULITIS AND THE DEVELOPMENT OF STENOSIS

Early in the course of rheumatic carditis the mitral valve is dilated, the valvular defect being minimal and nondeforming. Whether and

8. (*a*) St. Lawrence, W.: Potential Cardiac Disease and Prevention of Organic Heart Disease in Children, J. A. M. A. **78**:747 (April 1) 1922. (*b*) Boone, J. A., and Levine, S. A.: The Prognosis in "Potential Heart Disease" and "Rheumatic Mitral Insufficiency," Am. J. M. Sc. **195**:764, 1938. (*c*) Bland, E. F., and Jones, T. D.: The Delayed Appearance of Heart Disease After Rheumatic Fever, J. A. M. A. **113**:1380 (Oct. 7) 1939.

when this initial dilatation has been superseded by organic stenosis is often difficult to determine in the individual case. Determination of the presence of mitral stenosis is perhaps of no practical importance, since as a rule death in childhood and early adult life can be attributed to active infection of the myocardium rather than to the degree of mechanical defect of the valve.[9] The appearance in early childhood of the adult type of mitral stenosis, with typical rumble and thrill, however, seems to make for an unfavorable prognosis.[10]

The middiastolic blow which is heard to the right of the apex during acute carditis appears early in the course of the disease, at a time when the valve is dilated rather than stenosed, and tends to disappear with subsidence of the infection. It seems to be of more value as an indication of active infection than as a clue to the presence of anatomic narrowing of the valvular orifice. In 24 known instances in the present series such a middiastolic blow became inaudible before recovery from the first attack. In 6 instances the murmur disappeared after the acute infection had subsided. Bland, White and Jones[11] have revived an earlier theory[12] to explain the origin of this murmur, namely, a comparative narrowing of the mitral valve, which is not stretched in proportion to the dilatation of the ventricle. The fact that a similar murmur is heard occasionally in the heart dilated as a result of the increased burden placed on the ventricles by anemia or the shunt of blood through a widely patent ductus arteriosus seems to serve as corroborative evidence in favor of this explanation. However, such a middiastolic blow is often noted in a rheumatic heart that is only slightly enlarged and may not be present in a heart showing a far greater degree of dilatation. The relative inelasticity of the acutely inflamed mitral leaflets should not be ignored. Such rigid edematous valves may open with comparative slowness and present a stenotic orifice for a short period in early diastole. Perhaps both valvular rigidity and ventricular dilatation, singly or in combination, may play a part in the production of the middiastolic blow heard during active rheumatic carditis.

Postmortem studies[11] in Boston of the hearts of patients with rheumatic infection who had died before the age of 21 years seem to

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9. (*a*) Rothschild, M. A.; Kugel, M. A., and Gross, L.: Incidence and Significance of Active Infection in Cases of Rheumatic Cardiovascular Disease During the Various Age Periods, Am. Heart J. **9**:586, 1934. (*b*) Werner, S. C.: Rheumatic Cardiac Disease: Association of Active Rheumatic Fever with Heart Failure, Arch. Int. Med. **57**:94 (Jan.) 1936.

10. (*a*) Findlay, L.: The Rheumatic Infection in Childhood, Baltimore, William Wood & Company, 1932. (*b*) Ash.[1]

11. Bland, E. F.; White, P. D., and Jones, T. D.: The Development of Mitral Stenosis in Young People, Am. Heart J. **10**:995, 1935.

12. Gossage, A. M.: Early Signs of Rheumatism of the Heart, Lancet **2**:523, 1909.

indicate that the ultimate development of extensive valvular deformity, with or without actual stenosis of the mitral orifice, probably requires a minimum of two years and in most instances a considerably longer period. Rothschild and associates [9a] found that within the second decade of life no more than 30 per cent of the rheumatic hearts seen at autopsy presented any degree of stenosis. In the third and fourth decades the incidence of stenosis had risen to 65 per cent.

In the present series the diastolic thrill and rumble of the adult type of mitral stenosis, with or without an associated systolic murmur, were noted in only 39 cases, excluding 6 in which aortic insufficiency with free regurgitation had existed prior to the appearance of the rumble (Flint murmur?). In 3 cases the murmur existed at the time the diagnosis of rheumatic infection was first made, there having been no preceding history of known illness. In the remaining 36 cases the shortest period which elapsed after the onset of infection before the

TABLE 5.—*Evolution of Mitral Diastolic Rumble in Thirty Patients Observed from the Onset of Rheumatic Infection*

Type of Development		No. of Patients
Insidious development; no preceding murmur		5
Preceding systolic and middiastolic blows		12
Disappearance of middiastolic blow; later appearance of rumble	2	
Gradual replacement of diastolic blow by rumble	10	
Early systolic blow which disappeared; later rumble		6
Preceded by middiastolic blow	3	
No middiastolic blow	3	
Early systolic blow; later appearance of associated rumble		7

murmur appeared was two years; the average period was five years. The appearance of the murmur was delayed for ten years or more in 5 cases. In 20 cases (55.5 per cent) the murmur was noted some time between the end of the second and the end of the fifth year after the initial manifestation. The average age at onset in the 39 cases was 6.7 years and the average age at the time of appearance of the mitral rumble 11.4 years.

The stenotic lesion had already appeared by the time of the first examination in 9 cases, in 6 of which there was a history of previous attacks of rheumatism or chorea. In 15 of the cases in which the patient was under continuous observation a diastolic rumble made its appearance without having been preceded by a middiastolic blow. In 10 of these cases there were also signs of mitral regurgitation. In 15 cases a middiastolic blow had existed previously. This blow disappeared in 2 cases, subsequently to be replaced by a rumble. In the remaining instances the diastolic blow gradually became converted into a rumble, usually variable in appearance at onset.

In only 5 of the 30 cases in which the patient was under observation from the time of the initial manifestation did a stenotic lesion appear without preceding evidence of regurgitation (table 5).

The isolated diastolic rumble of pure mitral stenosis was noted in 15 cases, in 7 of which it was known that a mitral regurgitant murmur was present earlier. In 3 cases the lesion had been present at the first examination. In 5 it had appeared insidiously, no preceding murmur having been noted. The average time of appearance after onset was six and three-tenths years, somewhat later than that in the entire group of cases of mitral stenosis.

As compared with the group as a whole, chorea was more common as an initial manifestation and polyarthritis less common in the cases in which mitral stenosis developed (table 6). In cases of pure stenosis the infection seemed to be of a milder form, since the death rate in these cases was 13 per cent as compared with a death rate of 33 per cent in the cases in which both stenosis and regurgitation were observed. This is in accord with the observations in Boston,[13] where it was found in a clinical study of 81 young patients who had acquired

TABLE 6.—*Relation of Type of Onset to Valvular Lesion in Cases of Rheumatic Infection in Childhood*

Type of Onset	Percentage of Total Group of Patients	Percentage of Patients with: Mitral Stenosis With or Without Insufficiency	Pure Mitral Stenosis	Aortic Insufficiency
Joint manifestations, with or without carditis	63.5	51.4	53.3	69.1
Carditis only	16.7	18.2	6.6	25.5
Chorea, with or without carditis	19.8	30.4	40.1	5.4

the physical signs of pure mitral stenosis that a relatively mild form of rheumatic fever appeared to favor the development of this particular lesion. This is perhaps another manifestation of the fact that the most severe types of rheumatic infection are associated with the most marked degrees of cardiac enlargement. When little dilatation exists at onset chronic progressive fibrotic changes within the valve would result in the most perfect examples of pure stenosis, whereas in a greatly dilated heart some degree of insufficiency of the mitral valve might persist despite progressive stenosis. Whether subclinical activity of the infection may be responsible for the insidious development of stenosis is an unsettled point.

THE SYSTOLIC SCREECH

A clue to the existence of active carditis is the presence of a peculiar, high pitched, whistling screech, likened by some to the call of a sea gull.[14]

13. Walsh, B. J.; Bland, E. F., and Jones, T. D.: Pure Mitral Stenosis in Young People, Arch. Int. Med. **65**:321 (Feb.) 1940.

14. Taussig, H. B.: Management of Children with Rheumatic Heart Disease, M. Clin. North America **18**:1559, 1935.

This screech is usually heard in the region of the apex as a component of the mitral systolic blow but may occasionally be audible over the entire precordial region. It is possible that the "bleat murmur" mentioned by Maliner [15] and said by him to be due to pericarditis is identical with the "sea gull screech." Still [16] expressed the opinion that the supervention of a musical character to the bruit of rheumatic endocarditis is a sinister omen which generally points to severe progressive endocarditis. In the present series note was made of such a systolic whistle in 48 cases, in all but 2 of which it was associated with acute carditis which terminated fatally in 6 instances. In 5 cases the patient died subsequently of rheumatic heart disease and in 3 of bacterial endocarditis, so that the total death rate was 30 per cent. In all but 5 cases the murmur had disappeared before subsidence of the acute carditis. In 5 cases in all of which well marked rheumatic heart disease and persistent low grade infection were present, this whistling murmur was retained for periods varying from two to nine years.

PERICARDITIS

A pericardial friction rub was the most ominous cardiac sign. Of 81 cases in which such a friction rub was heard, 75 per cent terminated fatally. In 25 of the fatal cases the pericarditis developed in the initial illness; in 23 it developed during a terminal recrudescence. In 60 per cent, therefore, death resulted during the illness in which the friction rub was first noted. The duration of life in the cases of the patients who died early averaged one and two-tenths months from the appearance of the friction rub, the limits of variation being one day to six months. In the cases in which the patient survived an attack of acute pericarditis but subsequently died of rheumatic heart disease the average duration after recovery was two and four-tenths years, with limits of one to seven years. In 13 cases the patient died within a period of less than two years. Of the survivors, 5 (25 per cent) were cardiac invalids.

The experience of others [17] confirms the poor prognosis after acute pericardial involvement. On the other hand, the analysis of data for an older group of patients by Massie and Levine [18] suggests that the

15. Maliner, M. M.: The "Bleat Murmur" and Its Association with Fibrinous Pericarditis, Arch. Pediat. **54**:591, 1937.

16. Still, G. F.: Common Diseases and Disorders of Childhood, ed. 4, New York, Oxford University Press, 1924.

17. (*a*) Holt, E.: Chronic Adhesive Pericarditis in Childhood, Am. J. M. Sc. **178**:615, 1929. (*b*) Schlesinger, B.: The Milroy Lectures (1938) on the Public Health Aspect of Heart Disease in Childhood, Lancet **1**:593 and 649, 1938. (*c*) Findlay.[10a]

18. Massie, E., and Levine, S. A.: The Prognosis and Subsequent Developments in Acute Rheumatic Pericarditis, J. A. M. A. **112**:1219 (April 1) 1939.

onset of acute rheumatic pericarditis in later life has a somewhat less ominous prognosis (table 7).

That acute rheumatic pericarditis in childhood may occasionally be benign is evidenced by the cases of 2 patients in the present series who recovered from initial attacks of pericarditis, with subsequent freedom from all manifestations of the disease and recession of cardiac signs. The average time elapsed since recovery in the case of the 20 living patients was seven years, with a range from one to fourteen years. In 10 cases the duration was greater than five years.

AORTIC INSUFFICIENCY

Aortic disease as a cardiac sign was second in order of severity to acute pericarditis. This observation is similar to the experience of Findlay [10a] and of Schlesinger.[17b]

TABLE 7.—*Outcome in Cases of Acute Rheumatic Pericarditis*

Author	Number of Patients Traced	Average Age at Onset of Acute Pericarditis, Years	Average Time Elapsed Between Pericarditis and Recovery or Death, Years	Immediate Mortality, Percentage	Total Mortality, Percentage	Complete * Recovery, Percentage
Holt [17a]	43	"Childhood"	½ to 4	....	48.8	0.0
Findlay [10a]	69	8.5	1 to 17	47.8	63.4	2.9
Schlesinger [17b]	62	"Childhood"	6	33.3	50.0	11.0
Massie and Levine [18]	104	19.6	7	16.3	45.2	28.8
Ash (present series)	81	8.3	9.7	60.0	75.0	2.5

* No evidence of heart disease on physical examination.

Aortic insufficiency developed in 110 cases, in 59, or 52 per cent, of which the patient died. In addition, a transitory diastolic blow to the left of the sternum was audible in 10 cases of acute carditis.

Chorea was comparatively rare as an initial manifestation (table 6). The rare association of chorea with aortic lesions as compared with its common association with pure mitral stenosis has been commented on by Findlay.[10a]

Aortic involvement made its appearance during the initial illness in 41 cases, this first attack proving fatal in 12 (29 per cent). Death occurred in subsequent recurrences in 15 cases (37 per cent). As a terminal manifestation aortic insufficiency was present in 18 cases, including the 12 cases in which death occurred during the first attack.

In 6 cases an aortic diastolic murmur made an insidious appearance during a phase of low grade activity of the infection. Inconstancy at onset was noted in 18 cases, the murmur appearing and disappearing with no seeming relation to the existence of other clinical or laboratory manifestations of rheumatic infection but eventually becoming constant.

In 11 cases the patient recovered from one or more attacks of rheumatic illness with a seemingly normal heart only to have persistent signs of aortic and mitral damage develop as the result of an acute recrudescence. In the case of 1 boy aortic insufficiency had appeared insidiously in the seeming absence of infection. Except for this case, there was some evidence of mitral disease in all of the cases in which the aortic valve became involved. In 57 cases a mitral lesion preceded the appearance of aortic disease (table 8).

COMMENT

The presence of clinically demonstrable heart disease is of less importance as a guide to the management of the child with rheumatic infection than evidence indicating the existence of active infection. Such infection may be present when the heart seems normal. Information of value in determining whether the inflammatory process is progressing or regressing may, however, often be secured by careful consecutive examination of the heart. Because of this fact and in order to determine the prognostic significance of certain cardiac signs, it was thought worth while in the present paper to make an analysis of the cardiac signs for a group of some 500 children with rheumatic infection who had been followed for an average period of nine and six-tenths years from onset.

TABLE 8.—*Data for One Hundred and Ten Cases of Aortic Insufficiency*

	Number of Cases	Deaths, Percentage	
		Total	Terminal *
Aortic insufficiency present during initial illness	41	65.8	29.2
Aortic insufficiency preceded by mitral lesion	57	49.1	7.0
Aortic insufficiency preceded by potential or possible heart disease	12	16.6	16.6
Total	110	51.8	16.3

* Signs of aortic insufficiency were noted during terminal illness only.

Thirty-eight per cent of these children presented no definite clinical evidence of cardiac damage as a result of the initial illness. It is probable that pathologic examination would have disclosed changes in the hearts of many of them indicative of rheumatic infection, possibly of minimal degree. In 19 per cent of this group for whom a diagnosis of valvulitis was not made at onset, definite valvular damage subsequently developed, which in 80 per cent, however, was the result of an acute recrudescence of the disease. The valvular damage which developed in 6 of them in the seeming absence of infection and after a prolonged latent period may be interpreted as due to continued subclinical activity of the infection or to progressive fibrosis in the healing stage of a valve which had failed to disclose its initial damage by clinical signs.

The vastly higher death rate for the children with obvious carditis at onset was to be expected and can be attributed to the severity of the myocardial involvement. The fact that the death rate for children with seemingly normal hearts at onset tended to be relatively low during subsequent recurrences indicates that such children were suffering from a milder form of rheumatic infection or had possessed or had attained greater immunity and decreased myocardial susceptibility.

Proper care at the time of the initial manifestation may perhaps exert a favorable influence on the degree of permanent cardiac damage and the future course of the disease. Since pathologic changes characteristic of rheumatic infection probably occur in many hearts which present no evidence of carditis on ordinary clinical examination, the care of the child ill with acute rheumatic infection and showing signs of so-called potential or possible heart disease should not differ from that of the child with clinical signs of cardiac involvement. Complete rest in bed should be maintained until all clinical and laboratory evidences of infection have disappeared. It is possible that to some extent the improvement in the course of rheumatic infection noted at the Children's Hospital, which has been more fully commented on in a previous paper,[2] is related to the increased care now given to the child with a first attack of rheumatic fever, regardless of the cardiac diagnosis, as well as to intensive follow-up supervision.

Disappearance of physical signs of heart disease occurred in 10 per cent of the children who had presented signs of cardiac damage after recovery from the initial infection. Minimal anatomic changes probably persist in many of these patients. If one bears in mind the insidious appearance of mitral stenosis in a few children who had shown no initial evidence of heart disease, it is to be expected that some patients in this group in which regression of cardiac signs has occurred will in the future show evidence of mitral stenosis.

The apical systolic blow which occurs early in rheumatic infection in association with some degree of cardiac enlargement is due to incompetence of the valvular ring. However, at such a stage of the infection autopsy practically never fails to reveal inflammatory changes in the leaflets of the mitral valve which are definite, even though nondeforming. Since the valvular ring at this time is dilated rather than stenosed, the presence of an apical middiastolic murmur is not an indication of anatomic stenosis but rather a manifestation of active infection. Such a middiastolic murmur may disappear with subsidence of the infection. The shortest interval before the appearance of the rumble of mitral stenosis in the present series was two years and the average interval was five years from onset. Its appearance was delayed for ten or more years in 5 patients, and, in fact, its presence was noted in less than 10 per cent of the entire group. In approximately half the cases no middiastolic blow preceded the appearance of the stenotic rumble.

The murmurs of both mitral stenosis and aortic insufficiency tended to be inconstant at onset. The appearance of the peripheral signs of aortic insufficiency as a rule was delayed for months or years after the appearance of the murmur, although in an occasional case cardiac and peripheral signs appeared simultaneously. Aortic stenosis was rare and supervened only after many years of insufficiency.

Acute pericarditis had the most ominous prognosis, followed in order of severity by aortic insufficiency (associated with a mitral lesion in all cases but 1) and combined mitral stenosis and insufficiency.

At the end of the period of observation one quarter of the children had died of heart disease, a third of the deaths having occurred within the first year of the infection. Sixty per cent of the group either had no heart disease or were not prevented by their cardiac damage from leading a normal existence.

SUMMARY

The cardiac signs for a group of 553 children with rheumatic infection observed over an average period of nine and six-tenths years since the onset of the infection have been described.

SALMONELLA SUIPESTIFER INFECTIONS IN CHILDHOOD

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The literature of the last few years shows that the number of reports on infections with Salmonella suipestifer is increasing. This increase is probably due to the fact that interest in these infections has awakened and it is an old rule that the more one seeks something the more often one finds it. Before commenting on the subject of the infections as a whole we wish to describe 6 cases.

Fig. 1 (case 1).—Roentgenogram, showing changes in the region of the left shoulder.

REPORT OF CASES

CASE 1.—This case was reported in detail in 1935 [1]; so we shall deal with it here only briefly. B. A., an 8 month old girl, was admitted to the hospital in November 1933 with the complaint of ill health for several weeks, inability to use the left arm and swelling in the region of the left shoulder. During this time the infant had continuous fever (temperature of 39 C. [102.2 F.]). Lancing the swelling yielded 5 cc. of pus, from which S. suipestifer was isolated. The swelling of the shoulder region began to increase; so it was incised, and a periarticular abscess containing 10 cc. of pus was drained. The roentgenogram made on admission showed periosteal thickening at the proximal metaphysis and a small area of rarefaction on the outer part of the upper end of the diaphysis of the

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1. Gajzágó, D., and Göttche, O.: Osteomyelitis Suipestifer, Am. J. Dis. Child. 49:1270 (May) 1935.

left humerus. The reactions to tuberculin and Wassermann tests were negative, the spleen was not enlarged and the blood picture was normal. The temperature fell after the abscess was drained, and the course was subfebrile for two weeks, after which the temperature was normal. The wound healed in three weeks, and the swelling decreased. The child began to move her left arm. The roentgenogram taken at this time (fig. 1) showed continued periosteal thickening and rarefaction of the bone. The child when discharged on December 17 was healthy. The follow-up examination three months later showed that recovery was complete, and the roentgenogram of the bones was normal. The periosteal thickening had disappeared.

The girl was the daughter of a gardener living in the country, but in the past year there had been no illness where the family was living, either among human beings or among animals. S. suipestifer was not recovered from either the feces or the urine of the parents, and their blood did not show agglutinins for this organism.

In this case there were mild osteomyelitis of the left humerus and fever for three weeks. After incision the temperature fell, and the process healed in one month. The infant was healthy before the swelling in the left shoulder region occurred; there had been no diarrhea or other illnesses. The infection with S. suipestifer was manifested only in the form of osteomyelitis.

Case 2.—M. M., an 8 month old girl, was referred to us with the complaint of illness of two weeks' duration, which began with fever and anorexia. The fever was irregular; sometimes the temperature rose to 39 C. (102.2 F.), and at other times it was normal. During the second week of the illness the parents observed that if the infant's right arm was held she cried but did not move it. The referring physician observed that the right arm hung down as though paralyzed; so he sent the infant to us with the diagnosis of suspected poliomyelitis.

The infant, who was well developed and well nourished, had weighed 3,500 Gm. at birth and now weighed 4,500 Gm. She was an only child. She had been artificially fed from her second month; the feedings consisted of milk and beef tea. The first examination showed that although the right arm hung down as though paralyzed she could move her fingers; the shoulder region showed little swelling but was very painful. The nervous system showed no pathologic changes; the reflexes were normal. The roentgenogram (fig. 2) showed an irregularly shaped area of rarefaction the size of a pea at the proximal metaphysis of the right humerus but no periosteal thickening. The blood picture was normal; the red blood cells numbered 4,780,000 and the white blood cells 10,600, with 50 per cent lymphocytes; the hemoglobin content was 95 per cent. The reactions to tuberculin and Wassermann tests were negative. Lumbar puncture yielded normal cerebrospinal fluid.

Lancing the swelling in the region of the right shoulder joint yielded only a few drops of turbid fluid from which no bacilli were isolated. There was agglutination with the antiserum of S. suipestifer in a dilution of 1:2,500. The temperature fell in six days, the swelling began to disappear and the girl began to use her arm. After four weeks the arm was clinically normal. The roentgenogram showed that although the structure of the bone became normal the cavity remained unchanged. At this time there was agglutination of the antiserum of S. suipestifer in a dilution of 1:640.

The patient's parents were poor peasants living in a village near Budapest, and there were no pigs around their house or in their neighborhood. The infant

had received only boiled milk. No one had been ill in their vicinity for several months. The bacteriologic examination of the feces and the urine of the parents gave negative results. The results of agglutination tests were also negative.

In this case there was mild osteomyelitis of the right humerus. The swelling was not very great, and there was not much pus; so an incision was unnecessary. The fever lasted two weeks, and the process healed uneventfully. Pain, which was intense before the swelling subsided, causing the infant to hold the arm as though it were paralyzed, resulted in a pathologic picture resembling that of poliomyelitis.

Fig. 2 (case 2).—Roentgenogram, showing changes in the region of the right shoulder.

Case 3.—P. M., an 11 month old girl, was referred to us Aug. 29, 1934, with the complaint of illness of four weeks' duration. Since the illness began with fever and anorexia, the physician had thought of influenza. Two weeks later the infant was taken to another physician, who made the diagnosis of bronchitis. At this time the parents observed that the infant was very restless and did not move her right arm, which hung down as though paralyzed. The referring physician had made the diagnosis of poliomyelitis.

The infant, who was well developed and well nourished, weighed 7,900 Gm.; she was the second child of her parents. The first child, who was 4 years old, was healthy. The patient had been breast fed for six months and then was fed cow's milk with coffee, vegetables and beef tea.

The right arm hung down as though paralyzed, but the region of the shoulder joint was swollen and was tender on palpation. The other organs did not show any pathologic changes. The spleen and the liver were not palpable, and the

reflexes were normal. Examination of the blood showed 3,860,000 erythrocytes and 10,400 leukocytes per cubic millimeter, with 30 per cent lymphocytes and a hemoglobin content of 60 per cent. The roentgenogram (fig. 3) showed an area of rarefaction the size of a pea at the proximal metaphysis of the right humerus with periosteal thickening around it. The swelling increased, so on the tenth day after admission to the hospital we lanced the swollen region and obtained 5 cc. of pus, from which S. suipestifer was isolated. The serum of the infant agglutinated the antiserum of S. suipestifer in dilutions up to 1:1,280. The temperature fell in two weeks, the swelling began to disappear and the child began to move her arm. In the fifth week the infant was discharged home clinically healthy. The roentgenogram was unchanged. There was agglutination with dilutions of antiserum up to 1:640.

Six months later, May 10, 1935, the child was readmitted with the complaint of renewed swelling of the right shoulder and high fever. We lanced the swelling and again obtained about 5 cc. of pus, from which S. suipestifer was isolated. The infant's serum agglutinated S. suipestifer antiserum in a dilution of 1:2,560.

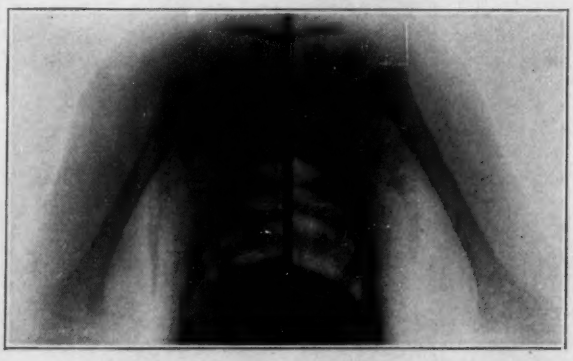

Fig. 3 (case 3).—Roentgenogram, showing changes in the region of the right shoulder.

The blood picture was the same as before. The roentgenogram of the right shoulder showed that the cavity was of the same size as six months before but that rickets had developed since then. The infant was in the hospital for four weeks. During this time the swelling entirely disappeared and the arm could be moved. She was taken home healthy. A roentgenogram showed marked decrease in the size of the cavity and healing of the rickets.

The infant's parents were of the poor working class and lived near Budapest. Seven persons lived in the home, which consisted of one room and a kitchen. There were no pigs in the house or in the neighborhood, and no one had been ill in the vicinity for several months. Bacteriologic examination of the feces and urine of all the persons who were living in the house and agglutination tests gave negative results.

In this case there was mild osteomyelitis of the proximal metaphysis of the right humerus. The process had also attacked the epiphysis, but the joint remained intact; only a periarticular abscess developed. This patient, like the one in case 3, was sent to us with the diagnosis of poliomyelitis because the pseudoparalysis of the right arm misled the physician. In this case the infection flared up again in seven months.

Case 4.—L. J., a 5 month old boy, was referred to us Feb. 19, 1936 with the complaint that swelling of the right knee region had begun five weeks before and had continued to increase. The right leg hung down as though paralyzed, was immobile and was painful on palpation. The temperature had remained normal. The referring physician had made a diagnosis of tuberculosis of the knee.

The infant, who was well developed and well nourished, weighed 5,300 Gm. and appeared normal except for the swelling of the right knee region. The reflexes were normal. The reactions to Wassermann and tuberculin tests were negative. Examination of the blood showed that the red cells numbered 3,680,000 per cubic millimeter and the white cells 12,200 with 55 per cent lymphocytes, and the hemoglobin content was 75 per cent. The roentgenogram (fig. 4) showed a cavity the size of a pea at the distal metaphysis of the right femur. There was

Fig. 4 (case 4).—Roentgenogram, showing changes in the region of the right knee.

no periosteal thickening. The swelling of the knee region was marked. We lanced the swelling and obtained 10 cc. of pus, from which S. suipestifer and Pneumococcus were isolated. There was agglutination with dilutions of S. suipestifer antiserum up to 1:1,280. Bacteriologic examination of the urine and feces gave negative results. The swelling disappeared slowly, and the boy began to move his leg; in four weeks he was taken home clinically healthy. The roentgenogram showed "consolidation" of the structure of the bone; the cavity was unchanged and periosteal thickening was still absent.

The infant was the sixth child of his parents, who were farmers. The parents and the other children were healthy, and none of them had been ill during the previous six months. There were many pigs on the farm, but none of them had been ill in the past several months. The bacteriologic and serologic examinations of the members of the family gave negative results.

In this case there was mild osteomyelitis of the distal metaphysis of the right femur. This was our first case in which the focus of infection was not localized in the humerus. This case was different from the

others also in that there was a mixed infection, Pneumococcus as well as S. suipestifer being isolated from the pus.

CASE 5.—L. J., a 5 month old boy, was brought to the outpatient clinic on Oct. 16, 1937 with the complaint of fever and restlessness of five days' duration. The boy was the first child of a charwoman, who lived near the hospital. The boy was well nourished and well developed. He had weighed 2,950 Gm. at birth and now weighed 6,600 Gm. The infant had been breast fed for three months, and since then he had received cow's milk with coffee, vegetables and beef tea. He was very restless, and slight opisthotonos was present. Lumbar puncture was performed, but the cerebrospinal fluid showed no pathologic changes. The roentgenogram of the chest was normal. A diagnosis of influenza was made. The child was brought back ten days later, on October 26, and the mother stated that fever had been continuous and the infant could not move his left arm. Examination showed that the left arm was tender on palpation, the reflexes were normal and swelling was not present. The roentgenogram showed normal conditions, so it was thought that a slight contusion was the cause of the pain.

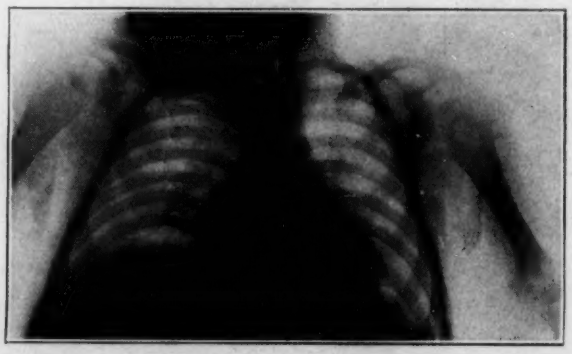

Fig. 5 (case 5).—Roentgenogram, showing changes in the region of the left shoulder.

The boy was brought back again on November 2. The mother stated that the condition had become worse, the temperature had not fallen and the infant could not move his left arm and was very restless. He was admitted to the hospital. The first examination showed that the left shoulder region was swollen and the left arm hung down as though paralyzed. The other organs showed no pathologic alterations. The infant did not give the impression of being very sick in spite of the high fever. The reactions to Wassermann and tuberculin tests were negative. Examination of the blood showed 3,520,000 red cells and 13,800 white cells per cubic millimeter, with 70 per cent lymphocytes and a hemoglobin content of 90 per cent. The roentgenogram (fig. 5) of the left humerus showed an alteration in the bone structure at the proximal epiphysis with the beginning formation of a cavity but no periosteal thickening. Lancing the swelling in the left shoulder region yielded 1 cc. of turbid fluid, from which S. suipestifer was isolated. There was agglutination with dilution of S. suipestifer antiserum up to 1:2,560. The infant appeared clinically healthy in four weeks, but a roentgenogram taken at that time showed a frank cavity in the involved region of the left humerus.

This was our first case in which the patient lived in Budapest. The mother was living in a typical tenement house. Seven adults and the patient lived in the home, which consisted of a kitchen and one room. One month before the beginning

of the patient's illness one member of the family, a charwoman, had had severe diarrhea, which she thought was caused by eating decayed pork. This was also our first case in which some one in contact with the patient had been ill. We do not know whether this woman had infected the infant, because the bacteriologic and serologic examinations both in her case and in that of the mother gave negative results.

In this case there was mild osteomyelitis of the proximal metaphysis of the left humerus. This case is interesting because the patient was observed by physicians in this hospital from the beginning of the illness, and it demonstrates how difficult the diagnosis is in the beginning, especially if one does not think of the possibility of osteomyelitis due to S. suipestifer infection.

CASE 6.—R. J., a 7 month old boy, was sent to us from the country by a physician, who wrote that he had been called to see the infant ten days before

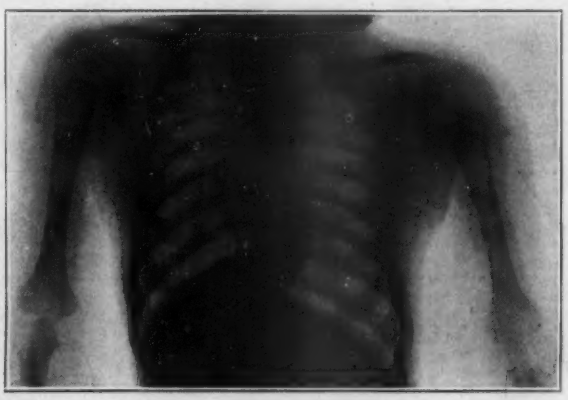

Fig. 6 (case 6).—Roentgenogram, showing changes in the region of the left shoulder.

because he could not move his left arm. There was swelling in the left shoulder region, and because the infant had no fever he thought that the shoulder might be dislocated. However, after a few days the temperature rose, and the physician referred the child to us with the diagnosis of "atypical arthritis."

After experience with our other 5 cases we thought immediately of the possibility of osteomyelitis caused by S. suipestifer. The left shoulder region was slightly swollen, and the mother said that the swelling had been more pronounced a few days before. Otherwise the child appeared normal. The reactions to Wassermann and tuberculin tests were negative. Examination of the blood showed 4,460,000 erythrocytes and 22,400 leukocytes, with 39 per cent lymphocytes, per cubic millimeter and a hemoglobin content of 90 per cent. The roentgenogram (fig. 6) showed slight periosteal thickening around the proximal metaphysis of the left humerus and an area of slight rarefaction just under the epiphysial line.

The mother informed us that the child had become ill four weeks before. The temperature had been high, ranging up to 40 C. (104 F.), and the physician had

Data from Cases of S. Suipestifer Infections in Childhood Reported in the Literature

Author	Year Illness Occurred	Country	Age of Patient	Outcome	Clinical Picture	Means by Which Organism Was Demonstrated
Dudgeon and Urquhart: Lancet **2**: 15, 1920	1920	England	12 yr.	Recovery	Typhus	Blood culture; agglutination tests
Wordley: Brit. M. J. **2**: 105, 1923	1923	England	13 yr.	Recovery	Typhus	Blood culture; agglutination tests
Nabarro, White, Dyke and Scott [4]	1929	England	8 mo.	Recovery	Bilateral osteomyelitis of the humerus	Culture of pus; agglutination tests
Bosch: Geneesk. tijdschr. v. Nederl.-Indië **69**: 42 and 462, 1929	1929	Netherland East Indies	11 mo.	Recovery	Purulent gonitis on the right side	Culture of pus; agglutination tests
Tenbroeck, Li and Yü: J. Exper. Med. **53**: 307, 1931	1931	China	6 yr.	Recovery	Paratyphus	Blood culture
Rau: Ztschr. f. Kinderh. **52**: 510, 1932	1931	Germany	7 mo.	Death	Gastroenteritis	Culture of blood and urine
Haynes [11].....	1931	United States	6 yr.	Recovery	Paratyphus	Blood culture
Kuttner and Zepp [3a]: Case 1	1931	United States	6 yr.	Recovery	Typhus	Blood culture
Case 2.....	1931	United States	11 mo.	Recovery	Typhus	Blood culture
Case 3.....	1931	United States	9 mo.	Recovery	Typhus	Culture of blood and feces
Case 4.....	1931	United States	7 mo.	Recovery	Typhus	Blood culture; agglutination tests
Case 5.....	1931	United States	4 yr.	Recovery	Typhus and pneumonia after whooping cough	Blood culture
Case 6.....	1932	United States	5 yr.	Recovery	Typhus	Blood culture
Case 7.....	1932	United States	4 yr.	Recovery	Typhus	Blood culture
van Creveld and Ruys [10]	1933	Netherlands	5 mo.	Recovery	Pneumonia; later, purulent gonitis on the right side	Culture of pus and feces; agglutination tests
Kuttner and Zepp [3b] Case 2.....	1933	United States	2 yr.	Death	Bronchopneumonia and sepsis	Blood culture
Case 3.....	1933	United States	19 mo.	Recovery	Purulent gonitis on the right side	Culture of pus; agglutination tests
Case 4.....	1933	United States	5 wk.	Recovery	Osteomyelitis on the right humerus	Culture of pus; agglutination tests
Bruin and Janssen: Maandschr. v. kindergeneesk. **2**: 533, 1933	1933	Netherlands	13 mo.	Recovery	Purulent gonitis on the right side	Culture of pus; agglutination tests
Gajzágó and Göttche: Case 1	1933	Hungary	8 mo.	Recovery	Osteomyelitis of the left humerus	Culture of pus; agglutination tests
Tevell: Orvosi hetil. **78**: 927, 1934	1933	Hungary	15 mo.	Recovery	Purulent arthritis of the articulation of the left humerus	Culture of pus; agglutination tests
Gouley and Israel: Arch. Int. Med. **53**: 699 (May) 1934	1933	United States	4 yr.	Recovery	Endocarditis; sepsis	Blood culture
Clifton and Werner [2]	1933	United States	10 mo.	Recovery	Bilateral subdural abscess	Culture of pus and cerebrospinal fluid; agglutination tests

Data from Cases of S. Suipestifer Infections in Childhood Reported in the Literature—Continued

Author	Year Illness Occurred	Country	Age of Patient	Outcome	Clinical Picture	Means by Which Organism Was Demonstrated
Gajzágó and Göttche: Case 2	1934	Hungary	8 mo.	Recovery	Osteomyelitis of the right humerus	Agglutination tests
Case 3.....	1934	Hungary	11 mo.	Recovery	Osteomyelitis of the right humerus	Culture of pus; agglutination tests
Tur and Gertoch [5]	1934	Russia	1 mo.	Recovery	Osteomyelitis of the right humerus; purulent gonitis on the right side; purulent arthritis of the ankle	Culture of pus; agglutination tests
Kun and Svastits [8]	1934	Hungary	4 mo.	Recovery	Osteomyelitis of the right humerus	Culture of pus(?)*; agglutination tests
Weaver and Sherwood [7]	1935	United States	9 mo.	Recovery	Bilateral osteomyelitis of the femur	Culture of pus; agglutination tests
Gajzágó and Göttche: Case 4	1936	Hungary	5 mo.	Recovery	Osteomyelitis of the right femur	Culture of pus †; agglutination tests
Case 5.....	1937	Hungary	5 mo.	Recovery	Osteomyelitis of the left humerus	Culture of pus; agglutination tests
Hinck [6]	1937	Germany	9 mo.	Recovery	Bilateral osteomyelitis of the humerus	Culture of pus; agglutination tests
Gagyi and Pomothy [9]	1937	Hungary	8 wk.	Recovery	Sepsis	Blood culture
Goeters: Monatschr. f. Kinderh. 75 : 27, 1939	1938	Germany	2 yr.	Recovery	Paratyphus	Blood culture; agglutination tests
Gajzágó and Göttche: Case 6	1939	Hungary	7 mo.	Recovery	Osteomyelitis of the left humerus	Agglutination tests

* Culture yielded both S. suipestifer and Haemophilus influenzae.
† Culture yielded both S. suipestifer and Pneumococcus.

thought of pneumonia. After a week the temperature dropped, but one week later the left arm seemed to be paralyzed.

Because of the mother's observation that the swelling was decreasing we did not lance it. There was agglutination with dilutions of S. suipestifer antiserum up to 1:2,560. The child was in the hospital four weeks, during which the swelling entirely disappeared and he began to move his arm. He was taken home entirely recovered. A roentgenogram showed no changes.

The parents of the child were living in a little village in the country. The father, a baker, kept pigs in his house, but they were healthy. There were three older children in the family, and neither they nor the parents had been ill in the past six months. Our patient was a well developed and well nourished boy who weighed 7,500 Gm. He had been breast fed for four months, after which he was given cow's milk with coffee, vegetables and beef tea. The milk was always boiled.

In this case there was osteomyelitis of the proximal metaphysis of the left humerus. The leukocyte count was higher in this case than in the others.

COMMENT

As we mentioned before, the number of published cases of S. suipestifer infections has shown a steady increase in the last few years. The infections were first observed to occur in small epidemics, caused by the ingestion of infected food, such as ice cream, pudding or raw milk. The symptoms of these infections were very similar to those of dysentery or typhoid fever. Later it was discovered that sporadic cases of infection with S. suipestifer also occurred. It was observed that S. suipestifer causes such different pathologic pictures as sepsis, pneumonia, pyelocystitis, meningitis and endopericarditis, and later observations showed that purulent processes frequently develop after infection with this organism. The organism was isolated from abscesses of the liver, from the pus of infected oviducts and from abscesses of uterine myomas. These observations refer to adults. Before dealing with S. suipestifer infections in childhood we should mention that such infections in adults are not very benign. Of the 311 cases of S. suipestifer infections in adults which Clifton and Werner [2] collected from the literature up to 1938, 19, or 61 per cent, terminated fatally. These data cannot be regarded as definitive, because we are convinced that thus far mostly cases of the more severe type have been reported and in those of the milder type other diagnoses have been made. The data collected thus far prove only that infections with S. suipestifer can be very dangerous, or even fatal.

We have been able to collect from the literature only 34 cases of S. suipestifer infections in children, including our 6 cases, although Clifton and Werner collected 36. The reading of all English publications is impossible in Hungary; so our conclusions refer only to the reports of cases which we were able to study ourselves. Data on these cases are given in the table. The geographic distribution of the reported cases was as follows: United States, 14 cases; Hungary, 9; England, 3; Netherlands (including the Netherland East Indies), 3; Germany, 3; China, 1, and Russia, 1. These reports show that S. suipestifer infections in childhood have been observed in almost all parts of the world. The fact that more cases were reported from some places than from others indicates only that such infections are being investigated more intensively in some areas than in others. As more pediatricians become aware of the infections more cases will be discovered and reported. At present obtaining definite data about the frequency of the infection is impossible. The fact that only 14 cases have been reported from the whole of the United States, 10 of which were reported by Kuttner and

2. Clifton, W. M., and Werner, M.: Infections with Salmonella Suipestifer (Hog Cholera Bacillus) in Childhood, Am. J. Dis. Child. **55**:553 (March) 1938.

Zepp [3] from Baltimore, and that of the 9 cases reported from Hungary we reported 6 from Budapest does not mean that more infections occur in Baltimore and Budapest but only that thus far they have been investigated more intensively in these two places.

In the 34 cases of S. suipestifer infections in childhood we collected from the literature the following clinical pictures were present:

Clinical Picture	Age of Patients Who Recovered, Years		No. of Deaths
	0 to 2	Over 2	
Typhoid fever or paratyphus	4	8	..
Sepsis	3	..	1
Dysentery	1	..	1
Subdural abscess	1	..	..
Osteomyelitis or purulent arthritis	17	..	..
Total	26	8	2

It is of interest that in 17 of these 34 cases of infections in childhood osteomyelitis developed after infection with S. suipestifer. The occurrence of such osteomyelitis has never been described in the case of an adult. It is even more interesting that 25 of the patients in the 34 cases were under 2 years of age and that the 17 who had osteomyelitis all fell in this age group. Thus 68 per cent of the children under 2 years of age who had infections with S. suipestifer had osteomyelitis. In 1935, when we reported our first case, we mentioned this interesting fact about age incidence, and later observations have confirmed it.

The next question is whether the osteomyelitis caused by S. suipestifer differs from that caused by other micro-organisms. It is well known that osteomyelitis in infancy differs in some degree from the similar pathologic processes which occur in later childhood. The most obvious difference is that in infancy the process is usually not so severe, so extensive or of such long duration as in later childhood. It is true that it more often extends to the epiphysis and involves the joint, but even in such cases there is quick recovery and unimpaired function of the joint is not a rarity. Purulent arthritis is mostly secondary in infancy; the infection starts in the metaphysis and involves the epiphysis and the joint secondarily. By osteomyelitis we mean all three processes, osteomyelitis, epiphysitis and arthritis, because the separation of these processes is not always easy and is not justified. Osteomyelitis in infancy caused by S. suipestifer is usually milder, from both the clinical and the

3. Kuttner, A. G., and Zepp, H. D.: (*a*) Bull. Johns Hopkins Hosp. **51**: 373, 1932; (*b*) Salmonella Suipestifer Infections in Man: Further Observations, J. A. M. A. **101**:269 (July 22) 1933.

roentgenographic point of view, than that caused by other pathologic micro-organisms. The clinical course of such osteomyelitis is as follows: The infant has fever from time to time, there is some weakness, and the appetite is impaired. At this time the examination will not reveal any pathologic changes, and the physician usually thinks of influenza as a diagnosis. The local symptoms usually develop during the second or third week of illness. The first symptom is tenderness of the involved extremity, which hangs down as though paralyzed, so that the condition resembles Parrot's pseudoparalysis of congenital syphilis. That was the reason that 2 of our patients were referred to us with the diagnosis of poliomyelitis. At this time the extremity is tender on palpation, and the infant is restless and cries a great deal. The swelling begins to develop in the third week. In cases of the milder form of the disease it may be so slight that one will easily overlook it. If the swelling is greater the formation of pus is also greater, but there is never much pus. In most cases a single lancing of the swelling is enough to evacuate all of the pus. The swelling was incised only in our first case; in 4 cases the swelling was lanced once and in 2 cases only 1 cc. of pus was obtained. In our last case the swelling was so slight that it was not necessary to lance it at all. The temperature usually drops during the fourth week, and the infant usually begins to move the extremity during the fifth week. The infant never gives the impression of being very ill, and the toxic symptoms which are common at the beginning of other types of osteomyelitis are always absent.

A more severe type of S. suipestifer osteomyelitis has thus far not been observed, but a milder form of the disease has been noted. In the case of Nabarro and associates,[4] in 1 case of Kuttner and Zepp and in 1 of our cases fever was absent and only local symptoms were observed It is therefore easy to understand why in our case the referring physician thought of the diagnosis of gonitis tuberculosa.

Several focuses may develop in the bones, as occurred in the cases of Nabarro and associates, Clifton and Werner, Tur and Gertoch [5] and Hinck.[6] It is worth mentioning that recurrences may be observed, as in our case 3, in which recidivation was manifested by sudden fever and the formation of a new abscess in the same place as the original focus seven months after apparent recovery from the infection.

In cases without complications the rest of the body shows no pathologic changes; enlargement of the spleen is infrequent.

Anemia, which is common with other types of osteomyelitis, is usually not present in cases of S. suipestifer infection. The behavior of the white

4. Nabarro, D.; White, P. B.; Dyke, S. K., and Scott, W. M.: Lancet **2**: 868, 1929.

5. Tur, A. F., and Gertoch, O. O.: Ztschr. f. Kinderh. **56**:696, 1934.

6. Hinck, O.: Ztschr. f. Kinderh. **53**:239, 1937.

blood cells is variable. In 5 of our 6 cases the blood picture was normal; in the sixth case leukocytosis was present. The blood picture is therefore not characteristic.

The roentgenographic changes are much less pronounced and much less extensive than those in cases of other types of osteomyelitis. The first roentgen sign is the appearance of a slight structural disturbance under the epiphysial line; later in this spot a cavity develops, usually a Brodie abscess no larger than a pea. The cavity usually appears during the third week of the illness and is most clearly observed from the fourth to the sixth week, when the clinical condition usually shows improvement. Periosteal thickening, which is one of the most characteristic symptoms of osteomyelitis, is usually slight and may be absent; in 3 of our 6 cases there was no periosteal thickening. In the cases thus far described only metaphyses were affected, and extension of the process into the diaphysis, with the occurrence of greater necrosis and more pronounced periosteal thickening, has not been described. Epiphysitis was observed only in our first case, in which the joint was not affected. In all of our cases only periarticular abscesses developed.

Some authors have reported the occurrence of arthritis after infections with S. suipestifer. Without denying the possibility of primary arthritis, we believe that in most cases such arthritis was secondary, if arthritis was the correct diagnosis. Roentgenograms have been included only in the report by Nabarro and associates; in all the other cases there were only descriptions of the roentgen changes, without illustrations; so we cannot be sure that we should have made the same diagnoses of the alterations as the authors. Nabarro and associates described the condition in their case as arthritis, but the published roentgenogram clearly shows osteomyelitis of the proximal metaphysis of both humeri. We mentioned this observation in our first communication, and it was confirmed by Weaver and Sherwood.[7]

The localization of the focus is also of interest. Thus far the following sites have been described: proximal metaphysis of the humerus, 13 cases; distal metaphysis of the femur, 8 cases, and distal metaphysis of the tibia, 1 case. In this list every focus is counted as a separate unit.

The bacteriologic and serologic aspects of S. suipestifer infections are too numerous for discussion here; we mention only that in the cases in which the pathologic picture was similar to that of typhoid fever, paratyphus or dysentery the organisms were demonstrated by blood culture or by agglutination tests, while in the cases in which purulent processes were present S. suipestifer was isolated from the pus. In 2 cases other organisms were also recovered. In the case of Kun and

7. Weaver, J. B., and Sherwood, L.: Hematogenous Osteomyelitis and Pyarthrosis Due to Salmonella Suipestifer, J. A. M. A. **105**:1188 (Oct. 12) 1936.

Svastits [8] Haemophilus influenzae was isolated first; it disappeared in four days, and then S. suipestifer appeared. Agglutination occurred with dilutions of S. suipestifer antiserum up to 1:3,200. In 1 of our cases S. suipestifer and Pneumococcus were isolated simultaneously and the agglutination test gave positive results with dilutions of S. suipestifer antiserum up to 1:1,280.

Another important question is how S. suipestifer infections occur. In 5 of our 6 cases the patient was a child of very poor peasants living in the country. In the cases of Kun and Svastits and Gagyi and Pomothy [9] the parents were vagrant gypsies, who, in 1 case, confessed that they had eaten the meat of dead pigs which they discovered. In the case of van Creveld and Ruys [10] pig merchants lived in the house where the parents of the sick infant lived, and a few of their pigs had died of some illness. Of the 10 patients of Kuttner and Zepp, 8 were Negroes. In the case of Weaver and Sherwood the 8 month old infant was fed raw milk from a cow which was ill. The 6 year old patient of Haynes [11] was living on a farm where many pigs were sick. Although in most of these cases the infection occurred in children who were living in the country, usually in the vicinity of pigs, and the parents were poor people with a low standard of living, the patients had not eaten pork in any form, and some of them had received only mother's milk. It is therefore impossible that the infection was caused by the ingestion of infected pig meat.

The investigations of Manninger and his associates [12] have thrown the most light on the epidemiology of S. suipestifer infections. They have shown that S. suipestifer is present in the gastrointestinal tract of at least 10 per cent of healthy pigs. If the pigs contract an infection or are subjected to external injury, hunger or exhaustion the bacilli not only increase in number but cause illness. In cases of pig pestilence the number of the organisms increases in the pigs, weakened by the virus of pig pestilence, and they may cause pathologic conditions which greatly resemble typhoid fever.

In the epidemics of human infection with S. suipestifer it is impossible that the disease was caused by the ingestion of originally infected food, because the foods incriminated were raw milk, puddings and ice cream, which must have been infected later by carriers of S. suipestifer. The newest observations show that healthy persons undoubtedly can be carriers of S. suipestifer. We believe that in our cases the patients'

8. Kun, L., and Svastits, P.: Orvosi hetil. **79**:827, 1935.

9. Gagyi, J., and Pomothy, R.: Orvosi hetil. **82**:1155, 1938.

10. van Creveld, S., and Ruys, A. C.: Ztschr. f. Kinderh. **54**:725, 1933.

11. Haynes, cited by Kuttner and Zepp.[3a]

12. Manninger: Lecture in the Academy of Science in Budapest, 1940, to be published.

parents, all of whom were living under bad economic and hygienic conditions, were infected either by infected pigs or by carriers of S. suipestifer and thus became themselves carriers of the micro-organism. The organism did not cause illness in them, but they passed it on to their children, in whom the bacillus did cause illness. Most of the patients were less than 2 years old; it is evident that age plays a very important role, since in 25 of the 34 cases we collected the patient was under 2 years of age. It is interesting to observe that in the families in which the infections occurred the parents and the older children remained healthy and only the youngest child became ill. It seems that infants and young children contract S. suipestifer infection much more easily than older children and adults because of their lower resistance.

S. suipestifer infection occurs much more often than was previously thought. If the possibility of its occurrence is kept in mind many interesting observations on this subject should be accumulated. One should not forget that although the subject of S. suipestifer infection is just now beginning to be investigated, enough data have been compiled to make further studies possible.

LONELINESS IN INFANTS

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NEW YORK

One of the most striking and at the same time one of the most obscure phenomena in pediatrics is the failure of infants to thrive in hospitals. The appalling infant death rate in American institutions within the twentieth century was recounted before this society by Dr. Chapin in 1915.[1] It seems hard to believe that only a quarter of a century ago the death rate for infants under 1 year of age in various foundling institutions throughout the country was nearly 100 per cent.

Happily this condition has been remedied and at present the mortality of foundling infants is relatively low, not so much because care in institutions has improved but because foundling homes have been in large part replaced by the much more suitable and less lethal foster homes.

Up to twenty or twenty-five years ago the failure of infants to do well in hospitals was attributed mainly to incomplete knowledge of nutrition. It is of interest that the most frequent diagnosis made in the infant wards in Bellevue Hospital for the decade following 1912 was malnutrition, for which condition a death rate of about 30 per cent was recorded. With the introduction and wider application of the newer knowledge of nutrition there was some decrease in the death rate, but infants continued to do poorly in hospitals.

Within recent years emphasis has been placed on infection as the important factor in infant mortality. At the present time nasopharyngitis instead of malnutrition is the most frequent diagnosis made in the infants' ward in Bellevue Hospital. "Hospitalism" is looked on as the result of repeated infections. Byfield,[2] writing in Abt's "Pediatrics," said that "hospitalism of infants is probably, in large part, little more than chronic infection." This is also the viewpoint expressed by the German pedia-

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Read before the American Pediatric Society, Hot Springs, Va., May 24, 1941.

From the Children's Medical Service, Bellevue Hospital, and the Department of Pediatrics, New York University.

1. Chapin, H. D.: A Plea for Accurate Statistics in Infants' Institutions, Tr. Am. Pediat. Soc. **27**:180, 1915.

2. Byfield, A. H.: Systemic Effects of Chronic Infection of the Upper Respiratory Tract, in Abt, I. A.: Pediatrics, Philadelphia, W. B. Saunders Company, 1923, vol. 3, p. 779.

trician Rominger,[3] who has stated, however, that such factors as adaptability of taste and drinking, excitement and diversion also play an important role in the personal care of the child.

To lessen the danger of cross infections, the large open ward of the past has been replaced by small, cubicled rooms in which masked, hooded and scrubbed nurses and physicians move about cautiously so as not to stir up bacteria. Visiting parents are strictly excluded, and the infants receive a minimum of handling by the staff. Within recent years attempts at isolation have been intensified, and a short time ago there was devised a box[4] equipped with inlet and outlet valves and sleeve arrangements for the attendants. The infant is placed in this box and can be taken care of almost untouched by human hands.

Cross infections unquestionably constitute a troublesome feature of infant care in hospitals. It is, however, reasonable to ask whether the measures used to prevent infection may not be harmful to the child.

Infants confined in hospitals present a fairly well defined clinical picture. A striking feature is their failure to gain properly, despite the ingestion of diets which in the home are entirely adequate for growth. Infants in hospitals sleep less than infants who are at home, and they rarely smile or babble spontaneously. They are listless, apathetic and look unhappy. The appetite is indifferent, and food is accepted without enthusiasm. The stools tend to be frequent, and, in sharp contrast with the habits of infants cared for in homes, it is unusual for twenty-four hours to pass without an evacuation. Infections of the respiratory tract which last only a day or two in a home often persist for months in a hospital. Return home results in defervescence within a few days and a prompt and striking gain in weight. An illustrative case is shown in figure 1.

M. K., a girl, was admitted to the hospital on June 18, 1940, at the age of 18 days, because she had had frequent watery green stools for four days. There was occasional vomiting, but the appetite was good. With treatment the diarrhea subsided promptly. The mother had congenital syphilis and a positive Wassermann reaction. The child had no symptoms of syphilis, and her Wassermann reaction was negative on numerous occasions after the second week of life.

The infant weighed 5 pounds and 6 ounces (2,438 Gm.) at birth. She gained fairly well at first, but when she was 15 weeks old fever developed and thereafter the gain in weight was slow. At the age of 8 months, when she left the hospital, her weight was only 9 pounds (4,082 Gm.), about one-half the expected weight for infants of her age and sex. From the age of 15 weeks until her discharge, when she was 8 months old, the temperature was elevated almost

3. Rominger, E., in Pfaundler, M., and Schlossman, A.: The Diseases of Children, English translation, edited by M. G. Peterman, Philadelphia, J. B. Lippincott Company, 1935, vol. 4, p. 160.

4. Chapple, C. C.: A Cabinet Cubicle for Infants, Combining Isolation with Control of Temperature and Humidity, J. Pediat. **16**:215, 1940.

daily. Usually the temperature ranged between 102 F. and 104 F. (39 to 40 C.), but on two occasions it rose to 106 F. (41.1 C.). No definite cause for the fever was ever found, except for a somewhat reddened pharynx and, on one occasion, a stomatitis. Repeated blood cultures, chemical and cytologic examinations and cultures of the urine, roentgenographic examinations of the chest and tuberculin tests gave negative results. The temperature failed to go down in response to sulfanilamide and some of its derivatives.

After the child's discharge from the hospital she showed a prompt gain in weight. She was seen six times after she left the hospital, the first time one week after discharge. Each time the temperature was below 100 F. (37.8 C.). Her weight at the end of 1 year was about 16 pounds (7,257 Gm.).

The mechanism of some of these symptoms can be readily understood but the basis for others is obscure. Infants even as young as 3 months normally smile and become animated in response to the pleasant

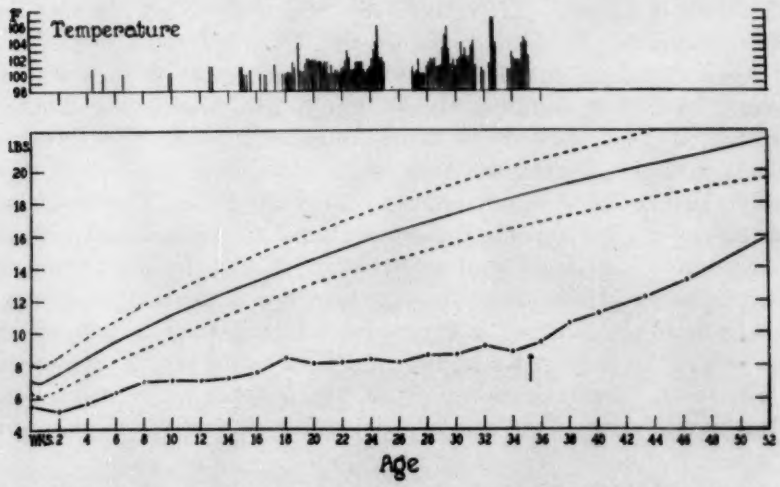

Fig. 1.—The temperature and weight curves of M. K. After her discharge from the hospital, indicated by the arrow, there were a prompt drop in the temperature to normal and a continued, steady gain in weight.

expression of an attendant. From most young infants who have been in a hospital even for a short time it is difficult to elicit a response in this way, and only after repeated attempts have been made does ready response appear. Presumably, psychologic neglect leads to a dulling of the reactivity of the children to emotional stimuli.

The failure of infants in hospitals to gain properly on diets calorically adequate for other infants is difficult to understand. It is true that infants in hospitals often gain fairly well on high caloric diets, but this does not account for the need for large amounts of food.

It is difficult to explain, on the basis of infection alone, the prompt gain in weight which takes place when the infants are returned to their

homes. This phenomenon is so constant as to be readily apparent even to young interns beginning a pediatric career. One would hardly expect that the effects of long-continued infection would disappear so promptly and constantly.

A striking example of recovery from the ill effects of confinement in a hospital was observed some time ago in Bellevue Hospital.

A. S., a boy, was the first-born child of healthy parents. Gestation and birth were normal and the weight at birth was 6 pounds and 14 ounces (3,118 Gm.). The child was breast fed for only three weeks and then, because of maternal illness, was removed from the breast and given artificial feeding.

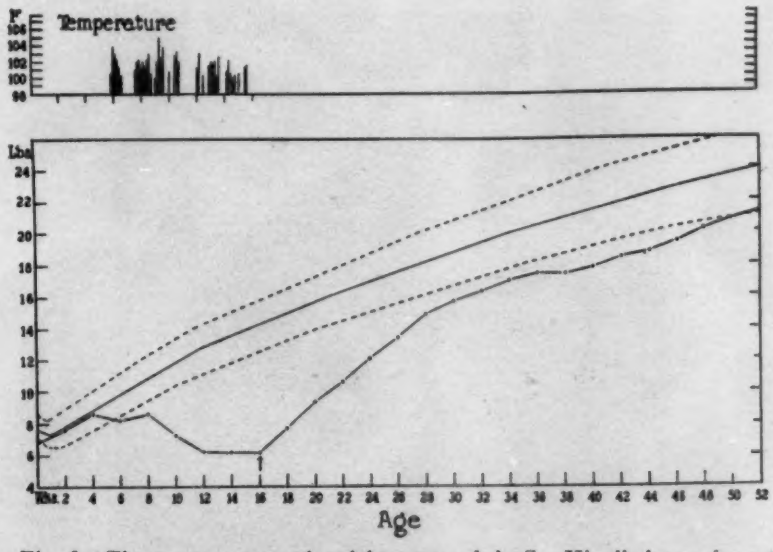

Fig. 2.—The temperature and weight curve of A. S. His discharge from the hospital, at the age of 16 weeks, indicated by the arrow, was followed by a drop in temperature and a prompt and rapid gain in weight.

He gained well at first and when 6 weeks old weighed 8 pounds and 14 ounces (4,026 Gm.). Shortly thereafter he had a nasopharyngeal infection accompanied with diarrhea and vomiting. He was admitted to the hospital at the age of 8 weeks. The gastrointestinal symptoms disappeared promptly with treatment, but infections followed each other in rapid succession. In spite of fairly large amounts of food, supplemented with accessory food substances and transfusions, the child went downhill rapidly. After eight weeks in the hospital, when he was 16 weeks old, the infant weighed 6 pounds (2,722 Gm.), almost a pound less than his weight at birth.

He was sick at this time, emaciated, wizened, pale and so weak that it seemed as if he might stop breathing at any moment. His mother, who had been visiting him several times a day, seemed to be so deft with him that it was decided to let her take him home. In the hospital the child had been receiving a breast milk feeding, about 65 calories per pound (453 Gm.) of body weight.

The feeding was changed to an isocaloric mixture of evaporated milk and cane sugar.

The effect of the home environment was well nigh miraculous. The child gained promptly, and he has continued to progress steadily up to the present. Now, at the age of 2 years, he is a normal, healthy, alert youngster. He weighs 30 pounds (13.86 Kg.).

A similar striking improvement in a child after discharge from an institution was reported by Chapin in 1908 [5] and is illustrated in figure 4.

That the ill effects on infants of confinement in hospitals are the result of psychologic neglect is by no means a new idea in pediatrics.[6] Parrot [7] the French clinician, who had a wide experience in foundling

Fig. 3.—*A*, A. S. at the time of discharge from the hospital. *B*, A. S. five weeks after leaving the hospital.

homes and in children's hospitals, came to the conclusion that the failure of children to survive in these institutions was due to lack of adequate stimulation. Czerny [8] felt that monotony and staring at blank walls

5. Chapin, H. D.: A Plan of Dealing with Atrophic Infants and Children, Arch. Pediat. **25**:491, 1908.

6. Freund, W.: Ueber den Hospitalismus der Säuglinge, Ergebn. d. inn. Med. u. Kinderh. **6**:333, 1910. Steinert, E.: Beiträge zur Frage des Hospitalismus und der Rolle der individuellen Pflege für das Gedeihen im Säuglingsalter, Ztschr. f. Kinderh. **28**:255, 1921.

7. Parrot, M., cited by Czerny, A.: Der Arzt als Erzeiher des Kindes, ed. 6, Leipzig, Franz Deuticke, 1922, p. 5.

8. Czerny, A., cited by Brennemann.[9]

and ceilings were important factors. Brennemann,[9] recognizing the effect of absence of mothering, established a rule in his hospital that every baby should be picked up, carried around, amused and "mothered" several times a day. Chapin,[10] who was responsible for the boarding-out system for the care of neglected children in America, was keenly aware of the need for psychologic stimulation, and he pointed out the need of babies for individual care and affection.

A recent report by Lowrey [11] throws some light on the nature of the trauma which results from prolonged residence in an institution. He studied a group of 28 children ranging in age from 2 weeks to 11 months at the time of their admission to an institution where they remained

Fig. 4.—The effect of removing a child from an institution to a home environment. E. K. weighed 9 pounds and 8 ounces (4,309 Gm.) on leaving the hospital (*A*), at the age of 13 months. Four months later (*B*) the weight was 18 pounds and 8 ounces (8,391 Gm.). Reproduced from Chapin.[5]

for two to three years. More than half had entered before they were 6 months old.

The clinical picture presented by these young children was similar to that seen in rejected children, but the personality distortion was

9. Brennemann, J.: The Infant Ward, Am. J. Dis. Child. **43**:577 (March) 1932.

10. Chapin, H. D.: Are Institutions for Infants Necessary? J. A. M. A. **64**:1 (Jan. 2) 1915.

11. Lowrey, L. G.: Personality Distortion in Early Institutional Care, Am. J. Orthopsychiat. **10**:576, 1940.

more marked. All the children showed symptoms of inadequate personality development, characterized chiefly by an inability to give or to receive affection and by noticeable insecurity. Certain behavior traits occurred frequently, such as hostile aggressiveness, temper tantrums (often of exceptional violence), enuresis, speech defects (sometimes amounting to near mutism), attention-demanding behavior, shyness and sensitiveness, eating difficulties (including refusal of food, fussiness and voracity), stubbornness and negativism, selfishness, finger sucking and excessive crying. Lowrey expressed the belief that the low level of speech development was due to lack of social stimulation and that this fact is important evidence of the "isolation" factor in the lives of these children.

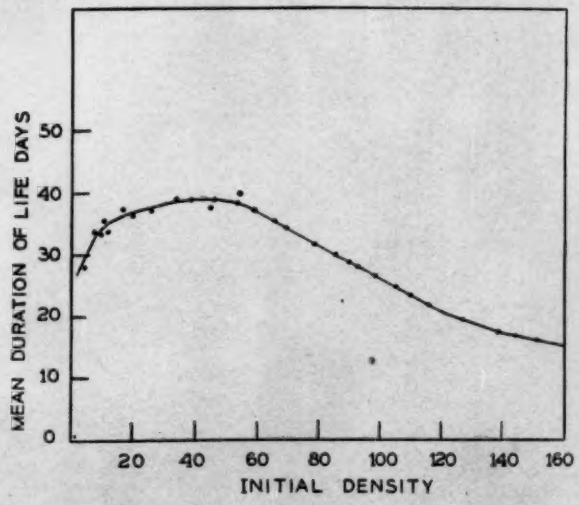

Fig. 5.—The relation between the initial density of Drosophila and the mean duration of life, after data by Pearl and co-workers.[13]

Three children who were placed in the institution after they were 2 years of age did not show the personality and behavior changes which were observed in the younger group, and Lowrey expressed a strong feeling that isolation during the early months of life is especially injurious.

There are several animal studies which demonstrate the ill effects of isolation on growth and longevity. Vetulani [12] observed the growth of inbred mice from the sixth to the twenty-second week and found that

12. Vetulani, T.: Untersuchungen über das Wachtum der Säugetiere in Abhängigkeit von der Zahl zussamengehaltener Tiere, Biol. gen. **7**:71, 1931; cited by Allee, W. C., in Murchison, C. A.: Handbook of Social Psychology, Worcester, Mass., Clark University Press, 1935, p. 919.

the isolated animals grew least, groups of 2 to 4 grew best, while larger groups gave intermediate values. Pearl and his co-workers [13] were able to show that the fruit fly does not survive as long when there are less than 35 members per ounce bottle as when there are 35 to 55 present. There is an optimal population density below which and above which the death rates at all ages are higher.

The title which I have chosen for this paper, "Loneliness in Infants," is perhaps dramatic, but I believe it expresses the essential problem created by hospitalization of infants. Human beings—all mammals and even lower forms for that matter—are social beings. Socialization is a basic mammalian pattern of behavior, and only psychotic persons are

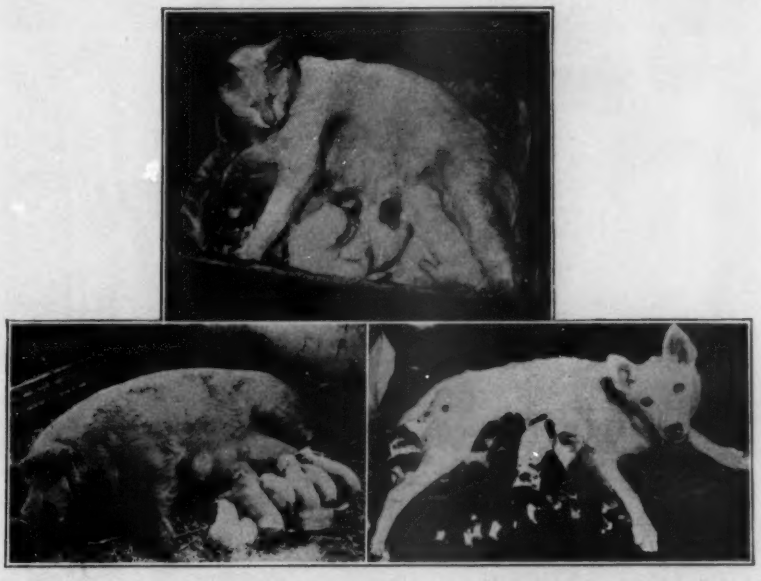

Fig. 6.—Mammalian care of the young (photographs reproduced by permission of Keystone View Company).

isolationists. Socialization begins early in life. Throughout the mammalian world, mother and offspring remain in close physical contact with one another during early postnatal life. One need but observe the cat with her kittens, the bitch with her pups, the sow with her sucklings, snuggling and cuddling together. Contrast this with the suggested methods for handling infants in the modern hospital (fig. 6). In the case of human beings one must recognize that during early life mother and babe constitute a biologic unit and if it becomes necessary

13. Pearl, R.; Miner, J. R., and Parker, S. L.: Density of Population and Life Duration in Drosophila, Am. Naturalist **56**:312, 1927.

to remove the infant from his mother a mother-substitute should be supplied.

It is not surprising, therefore, that the young infant should suffer when deprived of the warmth and security which he derives from contact with the mother or a substitute. Nor is it to be wondered at that the younger the infant the more important is this contact. The young infant is dependent on the environment for gratification of his psychologic needs just as he is for satisfaction of his nutritional needs. Only during the later months of the first year does he acquire a certain degree of independence. And just as the young infant has relatively few

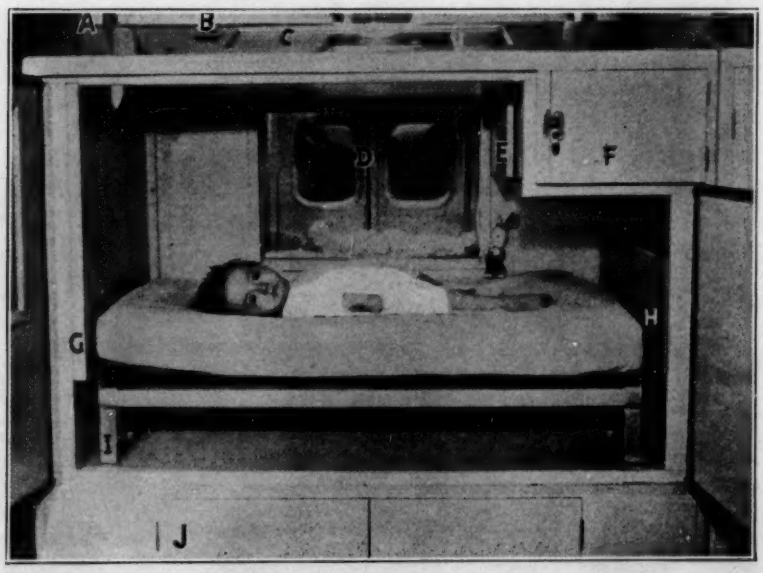

Fig. 7.—Device for isolating infants in hospitals from infection (reproduced from Chapple [4] by permission of the *Journal of Pediatrics*).

nutritional reserves within himself to fall back on during a period of starvation, so he has little in the way of psychologic resources to use when he is deprived of gratification of his psychologic requirements. The infant lacks the mental equipment which permits the adult or even the older child to tide over periods of loneliness by day-dreaming and planning for the future. In this respect, as in many others, he resembles the aged person, for whom also loneliness may be fatal. I refer to the frequent reports of death of an aged person shortly after the death of the husband or wife. Hans Zinsser,[14] in describing the death of the

14. Zinsser, H.: As I Remember Him: The Biography of R. S., Boston, Little, Brown & Company, 1940.

mother of R. S., two weeks after the death of the father, wrote: "She had grown more feeble for no physically noticeable reason. She seemed to die of his death."

A number of measures have been introduced in the children's service at Bellevue Hospital in an effort to supply substitutes for mother care. Mothering and cuddling are as much a part of the nursing care of the baby as are bathing and dressing. Interns are encouraged to pick up and play with the babies during their free moments. Infants who remain in the hospital for prolonged periods are assigned to particular interns for their special care. The parents of sick infants, instead of being excluded, are invited to the ward and are encouraged to hold and fondle their babies.

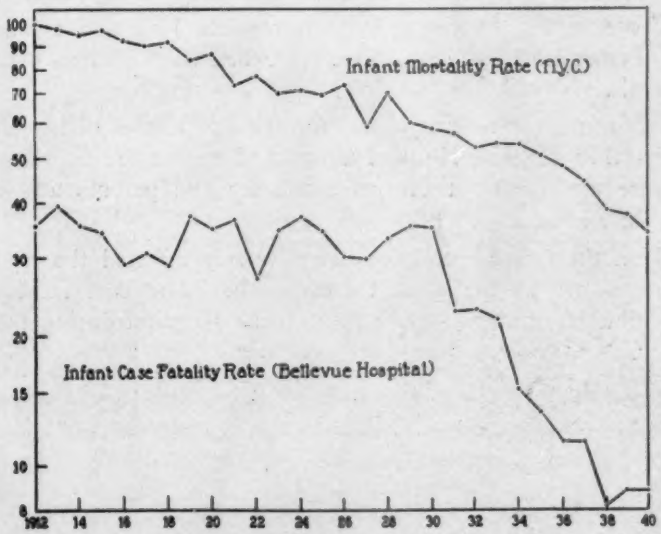

Fig. 8.—The case fatality of infants under 1 year of age in the children's medical service of Bellevue Hospital, 1912 to 1940. The upper curve represents the infant mortality rate for New York city (deaths of infants under 1 year per thousand births). The lower curve represents the infant case fatality rate at Bellevue Hospital (deaths of infants under 1 year per hundred admissions). The curves are plotted logarithmically so that the rates of fall can be compared.

The freer manipulation of the infants increases the possibility of cross infection. That the measures employed in Bellevue Hospital have not adversely affected the health of the infants is indicated by the trend of mortality in the infants' ward during the past thirty years.[15] Between 1912 and 1929, the case fatality rate for infants under 1 year of age was fairly constant, varying from 30 to 35 per cent and occasionally rising higher. Beginning in 1930 there has been a steady drop, to less than

15. Bakwin, H., and Turner, R.: Unpublished data.

10 per cent for the last three years. The factors producing this gratifying change are too complex for discussion here. The point which I wish to make now is that humanizing the hospital care of infants has not increased the mortality in the wards.

SUMMARY

1. Despite the improvement in knowledge of nutrition and the better isolation against infection, infants continue to do poorly in hospitals.

2. Pediatricians have long recognized that failure of infants to thrive in institutions is dependent, for the most part, on lack of the kind of stimulation which they normally receive in homes from their mothers. Infants in hospitals are lonely.

3. Some of the devices recently introduced to guard against the spread of cross infections have increased further the loneliness of infants in hospitals.

4. In an attempt to compensate for the deficiencies of hospitals in this respect, in Bellevue Hospital nurses and interns are encouraged to manipulate the infants at every opportunity and parents are invited to visit their infants.

5. That these measures have not adversely affected the health of infants is shown by the marked drop in the infant case fatality rate in the children's medical service of Bellevue Hospital during the past ten years.

MENINGITIS DUE TO ESCHERICHIA COLI

REPORT OF TWO CASES WITH RECOVERY FOLLOWING CHEMOTHERAPY, REVIEW OF THE LITERATURE AND REPORT OF EXPERIMENTAL STUDIES

GEORGE S. BARRETT, M.D.

CHARLES H. RAMMELKAMP, M.D.

AND

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Meningitis caused by the coli-aerogenes group of organisms occurs not too infrequently, and it is therefore somewhat surprising to find that little has been added to the knowledge of this disease since Macaigne [1] reviewed 5 cases in 1892. The lack of interest in this type of meningitis is even more difficult to understand in view of the fact that considerable progress has been made in the treatment of other types of meningitis. The failure to report in detail the history and clinical course of the illness, as well as the inadequacy of the available bacteriologic data, may be in part responsible for this apparent lack of interest.

Meningitis due to the colon bacillus has almost invariably been fatal in the past. It seemed desirable, therefore, to review the available case reports in the literature, to add 2 cases in which recovery followed the administration of sulfanilamide and some of its derivatives and to present certain experimental observations on the action of these drugs on the organism in spinal fluid.

REPORT OF CASES

Meningitis Due to Escherichia Coli Var. Acidi Lactici.—In 1921 Greenthal [2] reported the first case of meningitis caused by this organism. Seven other cases have been reported, 1 each by Sherman,[3] Ray,[4] Pasa-

From the Robert Dawson Evans Memorial and the John C. Haynes Memorial, of the Massachusetts Memorial Hospitals, and the Departments of Pathology and Medicine, Boston University School of Medicine.

1. Macaigne, M.: Le bacterium coli commune. Son rôle dans la pathologie, Thesis, Paris, no. 174, Paris, Société d' éditions scientifiques, 1892, p. 137.

2. Greenthal, R. M.: Case of Meningitis Due to Bacillus Acidilactici, Am. J. Dis. Child. **21**:203 (Feb.) 1921.

3. Sherman, D. H.: A Peculiar Case of Purulent Meningitis in the Newborn, Tr. Am. Pediat. Soc. **34**:192, 1922.

4. Ray, H. M.: Fatal Case of Bacillus Acidilactici Meningitis with Autopsy Findings, and Review of Bacillus Mucosus Infection, J. Lab. & Clin. Med. **8**:260, 1922.

choff,[5] Craig and MacKenzie [6] and Magarey, West and Pellew [7] and 2 by Fothergill and Sweet.[8] Sherman [3] thought the condition in his case was caused by Aerobacter aerogenes, but the accompanying data, while not complete, definitely place the organism with the acidi lactici type. The only previous case of this type in which recovery took place was that presented by Magarey, West and Pellew.[7] The patient was a 21 year old woman who had meningitis after a miscarriage at four months and was treated with methenamine and with lumbar and cisternal drainages. The first of the 2 cases herein presented makes the ninth reported case of this type and the second in which there was recovery.

CASE 1.—*Complete recovery of patient with meningitis due to Esch. coli var. acidi lactici following therapy with sulfanilamide and derivatives.*

TABLE 1.—*Cases of Meningitis Due to Esch. Coli Var. Acidi Lactici*

Author	Portal of Entry	Age	Outcome	Treatment
Greenthal [2]	Middle ear	1 month	Died	Supportive
Sherman [3]	Unknown	1 week	Died	Supportive
Ray [4]	Unknown	55 years	Died	Supportive
Pasachoff [5]	Unknown	10 days	Died	Supportive
Craig and Mackenzie [6]	Unknown	Newborn	Died	Supportive
Magarey, West and Pellew [7]	Septic abortion	21 years	Recovered	Daily lumbar puncture, cisternal punctures, methenamine and coramine
Fothergill and Sweet [8]	Unknown	2 weeks	Died	Supportive
Fothergill and Sweet [8]	Unknown	8 days	Died	Supportive
Barrett, Rammelkamp and Worcester	Unknown	6 years	Recovered	Sulfanilamide Sulfathiazole

History and Examination.—A 6 year old girl entered the John C. Haynes Memorial in a comatose state on July 13, 1940. The illness began with coryza eight days before entry. On the third day of the illness a cutaneous eruption appeared which was apparently typical of measles. Shortly thereafter she became listless, lost all appetite for food and gradually lapsed into coma. Her temperature during this period reached 102 F. on several occasions.

5. Pasachoff, H. D.: Meningitis Due to Bacillus Acidilactici in Newborn Infant, Am. J. Dis. Child. **41**:862 (April) 1931.

6. Craig, J. D., and Mackenzie, L. L.: Bacillus Acidilactici Meningitis in a Newborn Infant, J. Pediat. **8**:434, 1936.

7. Magarey, R.; West, L. R., and Pellew, R. A. A.: Cerebrospinal Meningitis Due to Bacillus Coli Infection Following Abortion; Recovery, M. J. Australia **2**:86, 1935.

8. Fothergill, L. D., and Sweet, L. K.: Meningitis in Infants and Children with Special Reference to Age-Incidence and Bacteriologic Diagnosis, J. Pediat. **2**:696, 1933.

Several months before entry she had an appendectomy. The pathologic diagnosis was early acute appendicitis. During the postoperative convalescence she had chickenpox.

Physical examination revealed a thin, comatose girl. The skin was warm, moist and pale. There was a dull brown eruption on the lower part of the abdomen, the back, the arms and the legs which was characteristic of the pigmented stage of measles. The throat was injected. The lungs were clear on auscultation, and the heart was normal in size on percussion. A systolic murmur was heard in the third left interspace. The neck was stiff and the back rigid. The biceps and the triceps jerks were equal and hypoactive. The abdominal reflexes and the knee and ankle jerks were absent. Kernig's sign was positive, and there was extension of the large toes on plantar stimulation.

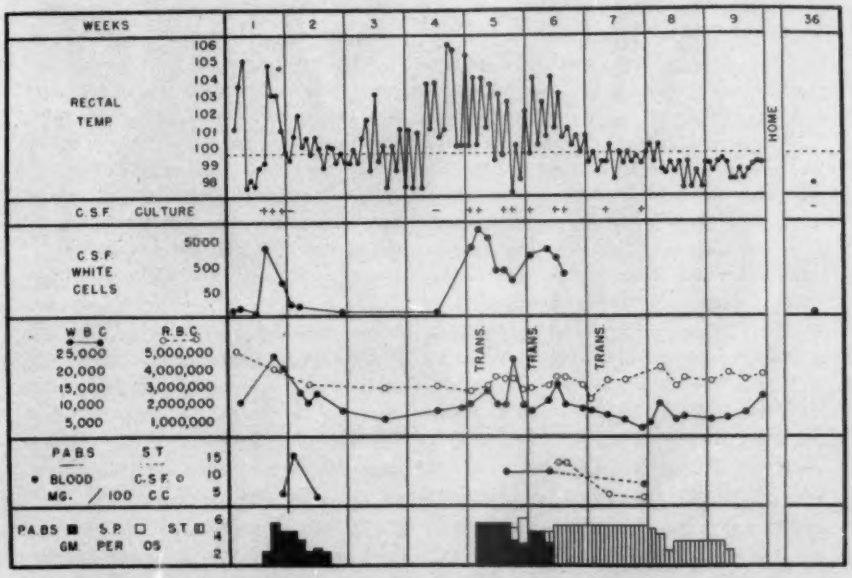

Chart 1.—Clinical course of patient with meningitis due to Esch. coli var. acidi lactici (case 1). P.A.B.S. indicates sulfanilamide (paraaminobenzenesulfonamide); S.T., sulfathiazole, and S.P., sulfapyridine.

On admission the white blood cells numbered 10,200 per cubic millimeter and the red blood cells 4,700,000. The hemoglobin content was 85 per cent. Examination of the urine showed a slight reaction for albumin and an occasional red and white cell in the sediment. A lumbar puncture showed an initial pressure of 160 mm. of water. The fluid was not cultured at this time; it was clear and contained 12 lymphocytes per cubic millimeter.

Clinical Course.—The clinical course is depicted in chart 1. After the administration of parenteral fluids the temperature returned to normal, but the spinal fluid pressure remained slightly elevated. On the fourth day the protein, sugar and chloride determinations on the spinal fluid were normal. On the fifth hospital day, the temperature rose suddenly; vomiting occurred, and the entire left side

of the body became spastic. There was an associated leukocytosis. The spinal fluid was now cloudy and contained 2,230 cells per cubic millimeter, of which 75 per cent were polymorphonuclear leukocytes. This fluid showed a pure culture of a gram-negative bacillus which was later identified as Esch. coli var. acidi lactici. Sulfanilamide therapy was instituted, and within three days the spinal fluid became clear. Analysis of the fluid on the eighth day of hospitalization showed a protein content of 36 mg. per hundred cubic centimeters and a sugar content of 52 mg. There were only 15 cells per cubic millimeter, all of which were lymphocytes. A culture of this spinal fluid was sterile.

On the eighth day of sulfanilamide therapy vomiting and diarrhea developed. Administration of the drug was discontinued because of these toxic symptoms and also because the patient showed signs of clinical improvement. She began to speak rationally and now recognized her parents. Improvement continued until the fourth week, when the temperature again became markedly elevated and a generalized scarlatiniform rash appeared. The throat was injected. As a precautionary measure 20 cc. of scarlet fever convalescent serum was administered. Cultures of blood and spinal fluid taken at this time were sterile. The neurologic examination showed a stiff neck and back, weakness and tremor of the left arm and leg, absence of abdominal and patellar reflexes and a Kernig sign bilaterally.

A lumbar puncture on the twenty-ninth hospital day again showed an increased pressure, of 270 mm. of water. The cell count of this fluid was elevated to 2,360 per cubic millimeter, of which 90 per cent were polymorphonuclear leukocytes. A smear showed gram-negative organisms, and the culture was again positive for Esch coli var. acidi lactici. The protein content was 160 mg. per hundred cubic centimeters and the sugar content 75 mg. Because of these observations sulfanilamide therapy was again instituted.

The clinical condition of the patient became rapidly worse during the fifth week. She became irrational, complained of a severe headache and vomited. By the end of the week, however, she began to show some symptomatic improvement. Daily lumbar punctures showed a gradual decrease in the number of white cells and the protein content fell to 53 mg. per hundred cubic centimeters, but cultures of the spinal fluid continued to grow the same colon organism. For the anemia that developed, she received one blood transfusion in that week and two more in the successive weeks.

In view of the fact that the spinal fluid remained abnormal, sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) was substituted for sulfanilamide, but such marked nausea and vomiting ensued that a return to sulfanilamide was made the following day.

In the sixth week she appeared somewhat worse and the spinal fluid cell count increased. Sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) therapy was substituted, with a resultant fall in temperature and satisfactory clinical improvement during the next few days. On the fourth day of sulfathiazole therapy the patient was able to sit up by herself for the first time. At the time of discharge, nine weeks after entry, the neurologic examination showed only a slight tremor of the left arm and leg. The reflexes were normal.

The patient returned thirty-six weeks later, at which time the lumbar puncture showed an initial pressure of 90 mm. of water. The fluid was clear, containing no cells or organisms. Neurologic examination showed no abnormalities.

Bacteriologic Studies.—The organism isolated on several occasions from this patient was a gram-negative, pleomorphic, nonmotile bacillus; it was present in large numbers on the original smear. It formed smooth pink colonies with blue

centers on eosin and methylene blue agar. The following reactions were exhibited by differential sugars:

Dextrose	AG	Arabinose	AG
Lactose	AG	Xylose	AG
Sucrose	O	Rhamnose	AG
Levulose	AG	Mannitol	AG
Galactose	AG	Salicin	O
Maltose	AG	Dulcite	O

The Voges-Proskauer reaction was negative, while the reaction to a methyl red test was positive. The serum obtained from the patient agglutinated her own organism to a titer of 1:160. No agglutinins were present for a strain of Esch. coli communis. Immunization of a rabbit with the patient's organism resulted in a titer of 1:1,280.

Summary.—A 6 year old girl entered the hospital with signs of meningitis. Cultures of the spinal fluid showed that the infecting organism was Esch. coli var. acidi lactici. Initially she was treated with sulfanilamide and daily lumbar punctures, which resulted in clinical improvement, a decreased number of cells in the spinal fluid and sterilization of the spinal fluid. Because of the development of vomiting and diarrhea administration of sulfanilamide was discontinued. The patient then apparently relapsed, and on administration of sulfanilamide for the second time she showed little improvement. Sulfapyridine therapy was attempted but caused nausea and vomiting. Sulfathiazole therapy, however, resulted in a rapid clinical improvement. Examination made thirty-six weeks after the onset of the illness revealed no abnormalities.

Meningitis Due to Esch. Coli Communis.—The first case of meningitis due to Esch. coli communis was that reported by Lloyd, in 1898.[9] No bacteriologic studies were recorded: only the statement that this was the organism isolated. Table 2 lists the 10 cases of this type which have been reported, in 2 of which there was complete recovery. Forbes[10] recorded the recovery of a child with spina bifida, but no details of the treatment are given, Tesdal[11] reported the recovery of a 23 year old woman whose first two lumbar punctures yielded a fluid that produced a pure culture of Esch. coli communis, while the fluid obtained at the third puncture was sterile. We are adding a third case, in which there was recovery from the acute infection although hydrocephalus subsequently developed.

CASE 2.[12]—*Recovery of an infant from meningitis due to Esch. coli communis followed by hydrocephalus.*

9. Lloyd, J. H.: Purulent Cerebrospinal Meningitis: Presence of the Bacillus Coli Communis in One Case, Internat. M. Mag. **7**:763, 1898.

10. Forbes, J. G.: The Pathology of the Cerebro-Spinal Fluid Derived from Lumbar Pressure, Quart. J. Med. **1**:109, 1907.

11. Tesdal, M.: Cured Meningitis Caused by Bacterium Coli Communis, Acta med. Scandinav. **83**:359, 1934.

12. Dr. George H. McGinnis granted permission to publish the details of this case.

History and Examination.—A 2 week old white boy entered St. Elizabeth's Hospital on July 2, 1941. There had been a midforceps delivery, and the infant appeared normal at the time of birth. Nothing unusual was noted until the tenth day, when he did not take his feedings. Examination at this time revealed nothing abnormal. The temperature was 99.5 F.; the leukocyte count was 15,000 per cubic millimeter. On the twelfth day the head was retracted slightly. On the fourteenth day the temperature reached 101 F. The neck was now definitely stiff; the fontanels were tense and all reflexes hyperactive. Kernig's sign was not present. A clinical diagnosis of meningitis was made.

On admission a spinal puncture was attempted, but no fluid was obtained. The ventricle was then tapped, and several cubic centimeters of a xanthochromic turbid fluid was removed. The cell count was 500 per cubic millimeter, of which 60 per cent were polymorphonuclear leukocytes. A direct smear of the fluid revealed no

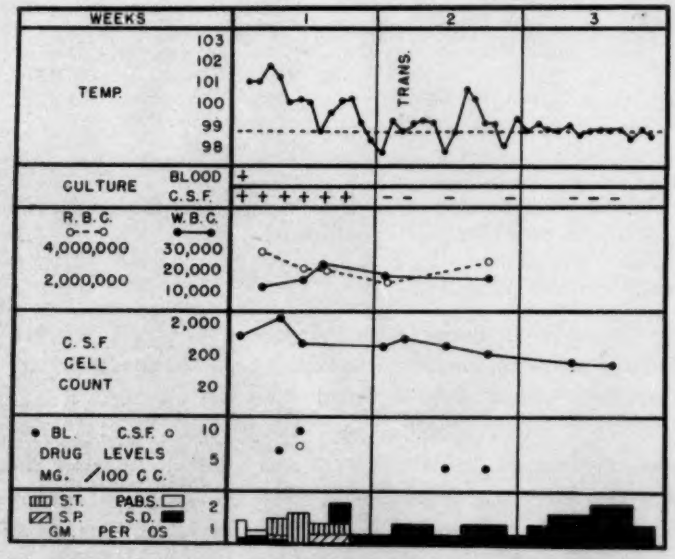

Chart 2.—Clinical course of patient with meningitis due to Esch. coli communis (case 2). S.T. indicates sulfathiazole; P.A.B.S., sulfanilamide; S.P., sulfapyridine, and S.D., sulfadiazine.

organisms. Cultures of blood and spinal fluid showed a pure growth of Esch. coli communis.

Clinical Course.—Chart 2 shows the course of this infant's illness while in the hospital. On admission a powder containing both sulfanilamide and sulfadiazine (2-[paraaminobenzenesulfonamido]-pyridine) was administered. On the third hospital day, after identification of the organism, sulfathiazole therapy was instituted. The ventricular fluid remained turbid, and the cell count was now 2,000 per cubic millimeter, 90 per cent of which were polymorphonuclear leukocytes. The protein content was 360 mg. per hundred cubic centimeters. A smear of this fluid showed gram-negative bacilli.

On the fourth hospital day the concentration of sulfathiazole in the blood and spinal fluid was 9.7 and 7.4 mg. per hundred cubic centimeters respectively. On the

fifth day the temperature fell to normal for the first time; however, the ventricular fluid continued to show an increased number of cells. The baby appeared less rigid, and twitchings of the face, which were noted soon after entry, became less frequent. On the sixth day sulfadiazine therapy was instituted and continued until the time of discharge. The first sterile culture of the ventricular fluid was obtained on the eighth hospital day. The infant showed a gradual decrease in the red blood cell count, and a transfusion was administered on the ninth day.

The patient continued to improve, gaining some weight and taking his feedings normally. The neck was not rigid; however, the fontanel remained tense and the head gradually enlarged. At the end of the third hospital week the child was transferred to the Boston City Hospital for observation. The spinal fluid remained sterile at this institution, and he was still living eleven weeks after the onset of illness.

Bacteriologic Studies.—The organism was studied by Miss Marion Lamb, of the Mallory Institute, Boston City Hospital, and was found to satisfy the requirements of Esch. coli communis, as indicated in table 3. No agglutination reaction was obtained between the organism and the patient's serum.

Summary.—In a 2 week old white boy signs of meningitis developed insidiously. Culture of the ventricular fluid on admission showed Esch. coli communis. Sulfanilamide, sulfathiazole and later sulfadiazine were administered until the spinal fluid became sterile, on the eighth hospital day, and subsequently the fluid remained free from organisms. A transfusion was given to combat an incipient anemia. Although the patient improved symptomatically, enlargement of the head developed. The child was still living eleven weeks after the onset of illness.

REVIEW OF THE LITERATURE

There have been several previous reviews of the literature on this subject, but the thesis by Ducasse [13] in 1925 is the only one containing an analysis of cases up to that time. In all the cases included in the present review there was an infection of the meninges caused by one of the organisms belonging to the coli-aerogenes group, and the organism was obtained in pure culture from the spinal fluid either during life or post mortem, or both. As far as possible, the bacteriologic data have been studied in each case and the organism classified according to present day standards. Although several of the early reports, especially those of Macaigne [1] and Scherer,[14] contained insufficient data for adequate bacteriologic classification, we feel that they cannot be excluded on the basis of the data presented.

Bacteriology.—In the English and foreign literature there are 108 cases of meningitis due to Escherichia coli or one of its types. A summary of these cases, including the 2 cases reported herein, is presented in table 2. In this table the cases are classified as to variety of infecting

13. Ducasse, P.: Méningite à coli-bacille chez le nourrisson, Thesis, Bordeaux, 1925-1926.

14. Scherer, F.: Ein Beitrag zur Aetiologie der Leptomeningitis purulenta bei Säuglingen, Jahrb. f. Kinderh. **39**:1, 1895.

TABLE 2.—*Cases of Meningitis Reported in the Literature*

Author	Date	Cases	Outcome *
Unclassified Esch. coli †			
Macaigne [1]			
Neumann and Schaeffer	1887	1	D
Roux	1889	1	D
Adenot	1889	1	D
Balp	1890	1	D
Sevester and Gasteau	1891	1	D
Sherer [14]	1895	3	3D
Huebner: Berl. klin. Wchnschr. **32**: 593, 1895	1895	1	D
Concetti [22]	1900	4	2R, 2D
Nobécourt, P., and du Pasquier: Gaz. hebd. de méd. **7**: 1153, 1902	1902	1	R
Goldreich, L.: Jahrb. f. Kinderh. **56**: 808, 1902	1902	1	D
Hartwich, W.: Berl. klin. Wchnschr. **48**: 795, 1911	1911	1	D
Holt [28]	1911	2	1R-C, 1D
Pearson, G. H.: Lancet **1**: 722, 1912	1912	1	D
Smith, E. B., and Woodforde, A. W. G.: Lancet **2**: 236, 1912	1912	2	2D
Dubois, M.: Scalpel **66**: 69, 1913	1913	1	R
von Reus, cited by Michael, M.: Arch. Pediat. **33**: 481, 1916	1914	1	D
Reiche, F.: Ztschr. f. Kinderh. **11**: 452, 1914	1914	1	D
Braillon and Merle, P.: Bull. et mém. Soc. méd. d. hôp. de Paris **37**: 332, 1914	1914	1	D
Milner, C. E. H.: Lancet **2**: 254, 1915	1915	1	R
Michael, M.: Arch. Pediat. **33**: 481, 1916	1916	1	D
Koplik [25]	1916	1	R-C
Lindberg [27]	1917	1	R-C
Arraud, cited by Ducasse [13]	1919	1	R
Theys and Gehrke: Virchows Arch. f. path. Anat. **246**: 318, 1923	1923	1	D
Dupérié, R., and Cadenaule, P.: J. de méd., Bordeaux **95**: 963, 1923	1923	1	D
Sickenga, F. N., and Munk, J.: Nederl. maandschr. v. geneesk. **12**: 179, 1923	1923	1	D
Rowe, O. W., and Kohlbry, C. O.: Am. J. Dis. Child. **29**: 287 (Feb.) 1925	1925	1	D
Neff [24]	1925	2	2R-C
Neal [18]	1926	5	1R-C, 4D
Reinhardt, I.: Monatschr. f. Kinderh. **36**: 341, 1927	1927	1	D
Braid, F. B.: Brit. M. J. **2**: 895, 1928	1928	1	D
Navarro, J. C.: Rev. de especialid. **4**: 211, 1929	1929	1	D
Bardisian, D. A.: Pediatria **38**: 777, 1930	1930	4	4D
Rhenter and Pizzera [21e]	1930	1	D
Vonderahe, A. R., and Bauriehter, F. X.: Ohio State M. J. **27**: 370, 1931	1931	1	D
Salvetti: Bull. Soc. de pédiat. de Paris **29**: 530, 1931	1931	1	R-C
Gibbens, J. B.: Lancet **1**: 1298, 1932	1932	3	3D
Rhenter and Dardaillon [21d]	1933	1	D
Fothergill and Sweet [8]	1933	4	4D
Jahkola [21a]	1935	1	D
Eckstein, A.: Diseases of the Meninges, in Pfaundler, M., and Schlossmann, A.: Diseases of Children, translated by M. G. Peterman, Philadelphia, J. P. Lippincott Company, 1935, vol. 5, p. 414	1935	1	R
Ratcliffe, T. A.: Lancet **1**: 1274, 1935	1935	1	D
Traissac, F. J.; Dutrenit, and Saric, R.: Bull. et mém. Soc. méd. et chir. de Bordeaux, 1936, p. 314	1936	1	D
Mulhern, M. E., and Seelye, W. B.: J. Lab. & Clin. Med. **21**: 793, 1936	1936	1	D
Hofmann, L.: Wien. med. Wchnschr. **86**: 774, 1936	1936	1	D
Crockford, A. L.: Brit. M. J. **1**: 1101, 1938	1938	1	D
Trillat and Notter [21c]	1939	2	2D
Thompson and Quinn [31]	1939	1	R
Meltzer, J.: Geburtsh. u. Frauenh. **1**: 718, 1939	1939	1	D
Cabot case 26,381 [19]	1940	1	D
Richardson, P. L., and Ranting, J. M.: Brit. M. J. **2**: 743, 1940	1940	1	D
von Wattenwyl, H.: Monatschr. f. Geburtsh. u. Gynäk. **110**: 342, 1940	1940	1	D
Hunt [20]	1941	1	D
Kohlbry [33]	1941	1	R
Total cases		75	
Esch. coli var. acidi lactici			
Greenthal [2]	1921	1	D
Ray [4]	1922	1	D
Sherman [3]	1922	1	D
Pasachoff [5]	1931	1	D
Fothergill and Sweet [9]	1933	2	2D
Magarey, West and Pellew [7]	1935	1	R
Craig and Mackenzie [6]	1936	1	D
Barrett, Rammelkamp and Worcester (case 1)	1941	1	R
Total cases		9	

TABLE 2.—*Cases of Meningitis Reported in the Literature—Continued*

Author	Date	Cases	Outcome *
Esch. coli communis			
Lloyd [9]	1898	1	D
d'Alloco, O.: Riforma med. **1**: 435, 1900	1900	1	D
Kovalevsky, O. V., and Moro, E.: Klin.-therap. Wehnschr. **50**: 1901	1901	1	D
Forbes [10]	1908	1	R
Smith, E. B., and Woodforde, A. W. G.: Lancet **2**: 236, 1912	1912	1	D
Barron [16]	1917	1	D
Rucks, W. L.: Memphis M. J. **6**: 155, 1929	1929	1	D
Tesdal [11]	1934	1	R
Mayers, M. M.: Urol. & Cutan. Rev. **41**: 16, 1937	1937	1	D
Barrett, Rammelkamp and Worcester (case 2)	1941	1	R-C
Total cases		10	
A. aerogenes			
Scheib, A.: Prag. med. Wehnschr. **25**: 169, 1900	1900	1	D
Beitzke, H.: Centralbl. f. Bakt. (Abt. 1) **37**: 496, 1904	1904	1	D
Noeggerath, C. T.: München. med. Wehnschr. **54**: 617, 1907	1907	1	D
Deane, A., and Shea, G.: Lancet **2**: 1237, 1928	1928	1	D
Shaw, F. W.: Virginia M. Monthly **58**: 248, 1931	1931	1	D
Fothergill and Sweet [8]	1933	1	R-C
Davis and Fernando [21b]	1935	1	D
Hensel, G.: Arch. f. Kinderh. **115**: 145, 1938	1938	1	D
Total cases		8	
Esch. coli communior			
Hinsdale [15]	1890	1	D
Total cases		1	
Atypical Esch. coli			
Anaerogenic coliform organism			
Rauch and Krinsky [32]	1940	1	R
Paracolon group similar to Esch. coli			
Frank [26]	1916	1	R
Cooke, J. V., and Bell, H. H.: Am. J. Dis. Child. **24**: 387 (Nov.) 1922	1936	1	D
Pochopien, F.: Polska gaz. lek. **4**: 63, 1938	1938	1	D
"Bacillus elasticum"			
Cooke and Bell: (See above)	1936	1	D
Total cases		5	

* D = Died. R = Recovered. R-C = Recovered with complications.

† J. N. Cruickshank (Child Life Investigations: The Causes of Neo-Natal Death, Medical Research Council, Special Report Series, no. 145, London, His Majesty's Stationery Office, 1930) reported 11 cases of meningitis from which coliform bacilli were isolated at postmortem examination. These are not included, as the author thought the organisms invaded the tissues during the agonal period.

organism. It is apparent from these figures that in the majority of cases the organism was listed as Bacillus coli, which makes accurate classification in the coli-aerogenes group impossible.

It is now generally considered necessary to combine the Voges-Proskauer and methyl red reactions with the sugar fermentations in order to classify this group of organisms correctly. Table 3 lists the essential sugars for the determination. Although Esch. coli var. acidi lactici is the largest type to be classified (9 cases), we do not believe it can be considered a leading member of the coli aerogenes group in the causation of meningitis, since it occurs only about one third as often as Esch. coli communis and Escherichia coli communior in routine laboratory examinations. A. aerogenes is also less frequently encountered than the two latter types. In view of the data presented, in the case

reported by Hinsdale [15] the organism called Escherichia coli immobile probably was Esch. coli communior. In 1935 Magarey, West and Pellew [7] reported a case in which they suggested that the organism might be Bacillus coli neapolitanis. It "is of the Bacillus coli group, but not communis. It does not ferment saccharose, is non-mobile and non-hemolytic." From table 3 it is obvious that the organism was more likely Esch. coli var. acidi lactici, and therefore we have included it in this classification. The three remaining types are oddities and do not appear in the accepted classification; hence they are included as special types.

Incidence.—A certain amount of confusion exists in the literature concerning the relative frequency of meningitis due to the colon bacillus. Barron,[16] in 1918 in an extensive review of meningitis in newborn and in young infants, found that in 33 per cent of all cases of meningitis in infants under 3 months of age Esch. coli was the cause. In 1927

TABLE 3.—*Essential Sugars for the Determination of Colon Bacilli*

	Dextrose	Lactose	Sucrose	Salicin	Dulcite	Voges-Proskauer	Methyl Red
Esch. coli communis	AG	AG	..	AG	AG	—	+
Esch. coli communior	AG	AG	AG	..	..	—	+
Esch. coli acidi var. lactici	AG	AG	..	..	..	—	+
Esch. coli neapolitanis	AG	AG	AG	AG	..	—	+
A. aerogenes	AG	AG	AG	AG	AG	+	—

Karplus [17] observed that in 30 per cent of the cases in her series the infecting organism was Esch. coli. On the other hand, in 1926 Neal [18] in her survey of 1,500 cases concluded that Meningococcus was the most common etiologic agent for this age group; there were only 3 cases in which the condition was due to Esch. coli. Fothergill and Sweet,[8] in an analysis of 705 cases of meningitis observed in children, found only 9 cases in which the disease was caused by the colon bacillus, in all but 1 of which the patient was an infant less than 4 weeks of age. Furthermore, their analysis revealed that the agents causing meningitis in newborn infants were restricted to three groups of organisms, namely, Streptococcus haemolyticus, Pneumococcus and the

15. Hinsdale, G.: Purulent Encephalitis and Cerebral Abscess in the New-Born Due to Infection Through the Umbilicus, Am. J. M. Sc. **118**:280, 1899.

16. Barron, M.: Meningitis in the Newborn and in Early Infancy, Am. J. M. Sc. **156**:358, 1918.

17. Karplus, D.: Die Meningitis des Neugeborenen, Wien. klin. Wchnschr. **40**: 250, 1927.

18. Neal, J. B.: Meningitis Caused by Bacillus of the Colon Group, Am. J. M. Sc. **172**:740, 1926.

colon bacillus, and that the last mentioned was the least frequent in this age group. This is in sharp contrast to Farber's more recent statement,[19] that Esch. coli is the most frequent cause of meningitis in infants under 1 month of age.

Age.—From table 4 it is noted that meningitis due to Esch. coli may occur at any age but that it is most common in infants under 3 months. Owing to the small number of patients in the other age groups, no conclusion can be made concerning the relation of age to mortality.

Portal of Entry.—In many of the cases the portal of entry is unknown. Table 5 summarizes those cases in which the portal of infection was

TABLE 4.—*Age Distribution of Patients with Meningitis Due to Esch. Coli*

Age Group	Number of Patients	Number of Recoveries	Mortality, Per Cent
Under 3 months	65	12	81
3 months to 1 year	11	5	55
1 to 25 years	16	5	69
25 to 50 years	7	1	85
50 to 75 years	6	1	83
Unknown	3	—	100

TABLE 5.—*Summary of Cases of Meningitis Due to Esch. Coli with Regard to Portal of Entry*

Portal of Entry	Cases
Unknown	54
Middle ear	13
Genitourinary tract (pyelitis 7, uterus 4, circumcision 1, prostate 1)	13
Gastrointestinal tract	12
Umbilicus	6
Spina bifida	2
Traumatic fracture of the skull	2
Miscellaneous (lung 2, gallbladder 2, orbit 1, joint 1)	6

determined. The middle ear and the genitourinary and the gastrointestinal tract are the most frequent portals of entry. In a study of Esch. coli bacteremia, Felty and Keefer [20] observed that the primary focus was usually the urinary tract, but their patients were all adults and no infections of the middle ear were noted. The cases in which the gastrointestinal tract has been recorded as a portal of entry have all been those of infants, and this tract was usually assumed to be the focus only because of vomiting and diarrhea. These are very common presenting signs in a wide variety of diseases afflicting infants, making the assumption a precarious one.

19. Colon Bacillus Meningitis, Cabot Case 26,381, New England J. Med. **223**: 465, 1940.

20. Felty, A. R., and Keefer, C. S.: Bacillus Coli Sepsis: Twenty-Eight Cases, J. A. M. A. **82**:1430 (May 3) 1924.

Although they have not been recorded in table 4, there have been several cases [21] in which the same organism which was found in the meninges was isolated from the urine and lochia of the mother. The most notable instance was that of Davis and Fernando,[21b] in which A. aerogenes was recovered in pure culture from both the infant and the mother. A primary hematogenous infection through the placenta suggests itself as the most probable mode of infection, but no blood cultures were made in these cases.

Mortality Rate.—The gross fatality rate in this series of cases was found to be 78 per cent. Twenty-four of the patients recovered from the acute infection. Nine of these subsequently had hydrocephalus; thus only 14 per cent recovered completely.

There was no correlation between the portal of entry and the prognosis. Age did not play an important role in the final outcome, as demonstrated in table 4. No definite statement can be made concerning which organism of the coli-aerogenes group is most virulent, since the total number of cases in any one group is too small to be significant.

Treatment.—Since an analysis of all the cases reported failed to show any correlation between the mortality rate and the age of the patient or the type of infecting organism, it is of some interest to review the therapy employed for those patients who recovered from the acute infection. Unfortunately, the details of treatment are lacking in the cases reported by Concetti,[22] Holt,[23] Tesdal,[11] Neff,[24] Koplik,[25] Frank,[26] Lindberg,[27] Forbes [10] and Fothergill and Sweet.[8] In cases in which

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21. (*a*) Jahkola, A.: Ueber die Meningitiden der Neugeborenen; zwei neue Fälle von Coli-Meningitis, Acta Soc. med. fenn. duodecim **23**:1, 1935. (*b*) Davis, L. J., and Fernando, F. S.: Meningitis Due to Mucoid-Encapsulated Bacilli: Report of Two Cases, Tr. Roy. Soc. Trop. Med. & Hyg. **29**:143, 1935. (*c*) Trillat, P., and Notter: Méningites aiguës à coli-bacilles chez le nourrisson, Lyon méd. **163**:624, 1939. (*d*) Rhenter and Dardaillon: Méningite à colibacilles chez un nouveau-né, Bull. Soc. d'obst. et gynéc. **22**:426, 1933. (*e*) Rhenter and Pizzera: Méningite aiguë suppurée à colibacilles, chez un nouveau-né de trois jours, ibid. **19**:559, 1930.

22. Concetti, L.: Sur les méningites aiguës non tuberculeuses chez les enfants, Ann. de méd. et chir. inf. **4**:765, 1900.

23. Holt, L. E.: Observations on Three Hundred Cases of Acute Meningitis in Infants and Young Children, Am. J. Dis. Child. **1**:26 (Jan.) 1911.

24. Neff, F. C.: The Leptomeningitides, in Abt, I. A.: Pediatrics, Philadelphia, W. B. Saunders Company, 1925, vol. 7, p. 555.

25. Koplik, H.: Meningitis in the Newborn and in Infants Under Three Months of Age, Arch. Pediat. **33**:481, 1916.

26. Frank, E. S.: Case of Paracolon Meningitis, Nederl. tijdschr. v. geneesk. **52**:888, 1916.

27. Lindberg, G.: Meningealblutung und eitrige Meningitis im frühen Säuglingsalter, Jahrb. f. Kinderh. **86**:363, 1917.

there was recovery before the advent of sulfanilamide and its derivatives the therapy included methenamine in 4 cases, artificial serum in 1, autogenous vaccine and saline solution directly into the ventricles in 1, electrargol (a colloidal silver preparation) in 2 and Vincent's serum intrathecally in another. It is difficult, however, to determine whether any of these therapeutic agents affected the course of the illness.

Complete details as to the number of lumbar or ventricular drainages are lacking in many of the cases in which cure was reported. However, of these 24 cases, in 12 there were frequent drainages, in 3 several and in 9 one or more. Although there is now a tendency in this country to perform few lumbar punctures in the treatment of meningitis,[28] it would appear that *frequent drainage might be beneficial in cases of meningitis due to the colon organisms.* Such reasoning is based not only on the results obtained in patients who recovered but also on the fact that Esch. coli and related organisms multiply in normal spinal fluid.[29] Concetti [22] recognized that normal spinal fluid does not constitute a favorable culture medium for microbes. Recently it has been found that the majority of organisms causing infection of the meninges will not grow in normal spinal fluid, nor will they grow in spinal fluid containing added amounts of serum proteins.[29] We have found that Staphylococcus aureus and Esch. coli grow readily in such mediums, although multiplication is somewhat slowed. These laboratory observations suggest, then, that frequent drainage of the spinal fluid might be of some benefit in patients with meningitis caused by staphylococci or colon organisms.

Of the 22 cases of meningitis due to the colon organisms reported since 1935, in 17 death occurred during the acute stage of the infection. It is interesting that in only 1 of these was sulfanilamide or one of its derivatives given.

Hunt [30] observed a 47 year old man who entered the hospital deeply jaundiced. Cultures of the blood and spinal fluid showed Esch. coli. Sulfanilamide, sulfathiazole and sulfadiazine were administered, and although the cultures of the blood and spinal fluid became sterile the patient died.

Five patients with meningitis due to Esch. coli have recovered since 1935 and all received chemotherapy. These include the 2 described herein and those treated with sulfapyridine by Thompson and Quinn,[31]

28. Hoyne, A. L.: Epidemic Meningitis, J.A.M.A. **115**:1852 (Nov. 30) 1940.

29. Rammelkamp, C. H.: Unpublished data.

30. Hunt, J.: Personal communication to the authors.

31. Thompson, H. E., and Quinn, R. P.: Meningitis Caused by Bacillus Coli, J. Iowa M. Soc. **29**:611, 1939.

Rauch and Krinsky,[32] and Kohlbry.[33] These results indicate, then, the definite value of the sulfanilamide group of drugs in the treatment of this type of meningitis.

EXPERIMENTAL STUDIES

In order to clarify the favorable effect noted in those patients treated with sulfanilamide and its derivatives, we made certain in vitro observations. In these studies the action of the various drugs on the colon bacillus was observed by the use of both urine and normal spinal fluid as culture mediums. In addition, an attempt was made to determine the concentration of drug necessary to obtain the maximal effect.

Previous studies [34] in our laboratory demonstrated that sulfathiazole was superior to sulfanilamide, sulfapyridine and sulfamethylthiazole (2-[paraaminobenzenesulfonamido]-4-methyl thiazole) in its inhibitory effect against gram-negative bacilli. Furthermore, sulfathiazole was found to be effective in concentrations as low as 5 to 10 mg. per hundred cubic centimeters when urine was used as the test medium.[35] In those studies broth, urine and whole defibrinated blood were used as culture mediums. More recently sulfadiazine has been found to be about equally effective against the gram-negative organisms when a semisynthetic medium is used.[36]

Methods.—Urine was collected from normal males and the p_H adjusted to 7.2. Spinal fluid was obtained both at the postmortem table and from lumbar punctures. The various drugs were added to samples of the urine and spinal fluid, after which sterilization was effected by passage through a Berkefeld filter. After the determination of the drug levels, the desired concentration was obtained by diluting with either normal spinal fluid or urine. The spinal fluid used in this study contained 25 mg. of protein, 95 mg. of sugar and 673 mg. of chlorides per hundred cubic centimeters.

The test organism, Esch. coli var. acidi lactici, obtained in case 1, was grown for twelve hours in plain broth. Dilutions of this culture were then made in either urine or spinal fluid, and 0.1 cc. of the various dilutions were added to 3 cc. of the spinal fluid medium or to 10 cc. of the urine. These dilutions were then incubated at 37 C.

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32. Rauch, S., and Krinsky, N.: Meningitis Caused by Bacterium Coli Anaerogenes (Anaerogenic Coliform Organism), Am. J. Dis. Child. **60**:1386 (Dec.) 1940.

33. Kohlbry, C. O.: Personal communication to the authors.

34. Rammelkamp, C. H., and Stoneburner, L.: Sulfathiazole: A Clinical and in Vitro Study of Its Use in Infections of the Urinary Tract, New England J. Med. **224**:45, 1941.

35. Vose, S. N., and Rammelkamp, C. H.: The Management of Urinary Tract Infections, M. Clin. North America **25**:1419 (Sept.) 1941. Rammelkamp and Stoneburner.[34]

36. Strauss, E., and Finland, M.: Bacteriostatic and Bactericidal Action of Sulfadiazine in Vitro on Gram-Negative Bacteria, Proc. Soc. Exper. Biol. & Med. **47**:432, 1941.

Samples were withdrawn at six, twelve and twenty-four hours, and after proper dilutions were made agar plates containing paraaminobenzoic acid were poured. The plates were incubated for twenty-four hours and the colonies counted.

Results.—Chart 3 shows the results obtained when urine is used as the test medium. In this experiment concentrations of sulfanilamide of 7.7 mg. per hundred cubic centimeters had little apparent effect on the growth of the colon bacillus, whereas concentrations as low as 1.9 mg. per hundred cubic centimeters of the other three test drugs caused definite bacteriostasis. Sulfathiazole was only slightly superior to sulfapyridine and sulfadiazine in these experiments.

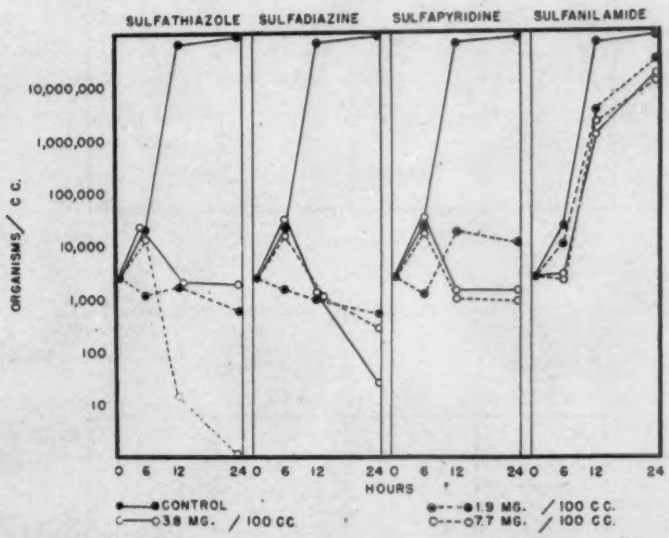

Chart 3.—Comparative actions of sulfanilamide and its derivatives in urine.

Chart 4 shows the results obtained when the drugs were added to spinal fluid in concentrations of 8.6 mg. per hundred cubic centimeters. In this experiment sulfathiazole appeared to be definitely superior to sulfanilamide, sulfapyridine and sulfadiazine.

It appears from the results reported that sulfathiazole was somewhat more effective than other available sulfanilamide compounds against Esch. coli. In other observations sulfadiazine caused bacteriostasis about equal to that caused by sulfathiazole.

Chart 5 demonstrates an experiment planned to show the effect of various concentrations of sulfathiazole in spinal fluid. A concentration of 1 mg. per hundred cubic centimeters showed only slight inhibition; however, a concentration of 4.3 and 8.6 mg. per hundred cubic centi-

meters exhibited marked bacteriostatic effect. It would appear from these experiments, then, that sulfathiazole was the drug of choice in the treatment of Esch. coli infection of the meninges and that concen-

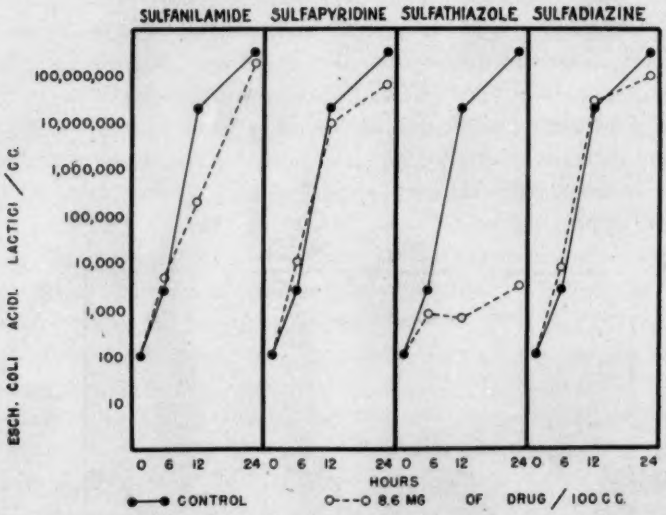

Chart 4.—Comparative actions of sulfanilamide and its derivatives in spinal fluid.

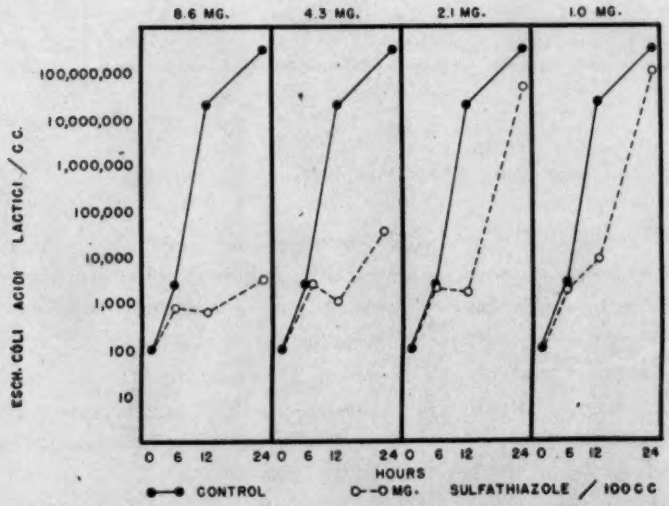

Chart 5.—Effect of various concentrations of sulfathiazole in spinal fluid.

trations of 4 to 10 mg. per hundred cubic centimeters in the spinal fluid are desirable in order to obtain the maximal effect.

COMMENT

In the past there has been considerable speculation concerning the pathogenesis of meningitis due to Esch. coli. It is evident from the reports that the infection in adults is produced either by direct extension or as one of several metastatic foci occurring during a period of bacteremia. It should be noted, however, that in the study of Esch. coli bacteremia in adults by Felty and Keefer [20] the meninges were not found to be a frequent site of secondary infection.

We have listed several of the common foci, such as the middle ear, the gastrointestinal tract, the umbilicus and the urinary tract. With the exception of infection through the middle ear, it is likely that the organisms infect the meninges after invading the blood stream. Although many of the authors have not recorded the results of blood cultures, Fothergill and Sweet [8] stated that in the majority of their cases there was a bacteremia. In several of the reported cases the mother harbored bacteria in the lochia and/or urine which were similar to the organism isolated from the meninges of the infected infant. A primary hematogenous infection suggests itself if such a focus is responsible. The role the gastrointestinal tract plays as a portal of entry is difficult to assess, since many infants have diarrhea during the course of metabolic disorders unrelated to meningitis.

The striking predilection of meningitis due to Esch. coli for infants under 3 months of age presents a matter for speculation. It seems probable that the newborn infant has little resistance to infection caused by the colon bacillus. This is supported by the observations of Ravid [37] that the blood of the fetus contains little or no agglutinins for the colon organisms. It would appear advisable, then, to give transfusions of whole blood to newborn infants with meningitis due to Esch. coli, thus adding the possible beneficial effect of antibodies.

In view of the work by Smith and Orcutt [38] on the resistance of calves to Esch. coli bacteremia, an attempt was made to correlate this with the types of feeding in the reported cases. They showed that a calf deprived of its mother's milk succumbs in a few days to septicemia due to Esch. coli. If colostrum is administered for several days, localization of the infectious process occurs, and the animal survives. Complete immunity is afforded by the continuous drinking of the colostrum. This work suggests that there is a protective substance in the colostrum!

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37. Ravid, J. M.: Meningococcic and Non-Meningococcic Meningitis in the Newborn and in Young Infants, Am. J. Dis. Child. **49**:1282 (May) 1935.

38. Smith, T., and Orcutt, M. L.: The Bacteriology of the Intestinal Tract of Young Calves with Special Reference to the Early Diarrhea ("Scours"), J. Exper. Med. **41**:89, 1925.

An analysis of the case reports on infants showed that 11 took breast milk soon after birth and in but a few instances was the child given cow's milk. Since many authors do not mention the type of feeding, it is impossible to conclude from this analysis on human beings that the mother's milk contains protecting substances.

The diagnosis of meningitis due to one of the coli-aerogenes bacteria is established by the culture and identification of the organism from the spinal fluid. The cerebrospinal fluid is usually turbid and always contains an increased number of cells. The total cell count is rarely above 10,000 per cubic millimeter and usually is under 3,000. Both polymorphonuclear and mononuclear cells are present, although the former usually predominate. In many cases the organisms may be seen on the direct smear of the fluid, and in these preparations the bacilli are both intracellular and extracellular. The protein content is somewhat elevated and the sugar content lowered.

Adults present typical symptoms and signs of meningitis and in addition usually show signs of generalized infection. In children and infants the diagnosis of meningitis due to Esch. coli is more difficult. The first symptom usually noticed by the mother is a failure of the child to nurse normally. The child becomes very irritable and at times may show spasm of the facial muscles. In such cases the diagnosis of tetany is occasionally made. In a few of the reported cases no other symptoms developed; however, most of the newborn infants begin to vomit their feedings and later exhibit convulsive seizures. The signs of meningitis, such as stiff neck, opisthotonos, increased reflexes, bulging fontanels and positive Kernig and Babinski signs, may be absent or may appear just before death. The temperature is not markedly elevated, only rarely rising above 101 F., and occasionally normal or subnormal temperatures are recorded throughout the illness. In a few cases the presenting symptom was hydrocephalus, and it was only after culture of the spinal fluid that a diagnosis was made.

From our in vitro studies it may be concluded that sulfathiazole is the drug of choice for infections of the meninges by members of the coli-aerogenes group of organisms. In order to insure maximum bacteriostasis concentrations between 4 and 10 mg. per hundred cubic centimeters should be obtained. However, it is well recognized that concentrations of sulfathiazole in the spinal fluid are variable despite adequate blood vessels. Although sulfadiazine did not appear to be quite as effective against the colon organisms in our experiments, recent experience suggests that it is almost comparable to sulfathiazole for the treatment of gram-negative infections of the urinary tract. A concentration in the spinal fluid of approximately two-thirds the blood level may be predicted, and it is probable that sulfadiazine may be equally effective.

SUMMARY AND CONCLUSIONS

Two cases of meningitis due to Esch. coli are described in which recovery followed therapy with sulfanilamide and derivatives. A review of the literature and experimental studies with Esch. coli in spinal fluid are presented. The following facts emerged from the study:

Meningitis due to Esch. coli is most common in infants under 3 months of age, and without chemotherapy the fatality rate is about 80 per cent.

The portal of entry may be obscure, but associated infections of the middle ear, gastrointestinal tract, urinary tract and umbilicus are recorded.

Bacteremia has been present in a number of cases in which blood cultures have been made.

The course tends to be protracted, with relapses and the development of hydrocephalus.

The spinal fluid continues to be infected for several weeks.

From experimental studies, it was learned that sulfathiazole in concentrations of 4 mg. per hundred cubic centimeters or higher was more effective than the other members of the sulfanilamide group.

It is suggested that sulfathiazole and repeated lumbar punctures are the methods of choice in treatment, since Esch. coli is one of the few organisms which can grow freely in cerebrospinal fluid and sulfathiazole is more effective than the other drugs of this group in inhibiting the growth of Esch. coli in cerebrospinal fluid. If an adequate concentration of sulfathiazole in the cerebrospinal fluid cannot be obtained, sulfadiazine should be administered.

It is also possible that whole blood transfusions in infants under 2 years of age may aid in treatment.

Dr. Louis Weinstein and Miss Eileen Sullivan assisted in this study.

HYPERTENSION AND PYELONEPHRITIS OF CHILDREN

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Hypertension has long been known to occur in certain cases of glomerulonephritis and in cases of chronic urinary obstruction. Not until comparatively recently, however, was hypertension reported in association with pyelonephritis. Löhlein,[1] in 1917, reported the cases of 2 young women who died of uremia; in each of these cases the blood pressure was elevated and there were only moderate amounts of albumin in the urine, with many leukocytes and no casts.

Quinby[2] apparently reported the first case of a child with hypertension and associated pyelonephritis. The patient was a boy 14 years of age. The blood pressure, measured in millimeters of mercury, was 250 systolic and 170 diastolic. A large, nonfunctioning, hydronephrotic right kidney was removed, after which the blood pressure fell to 138 mm. of mercury systolic and 90 diastolic.

In 1937 Butler[3] reported a series of 15 cases; 6 of the patients were dead, and 9 were living. The ages of the patients ranged from 3 to 11 years. Pyelonephritis and hypertension were demonstrated over a period of years before there was appreciable diminution of renal function. Butler pointed out that there was no positive proof that pyelonephritis had preceded hypertension. Five of these cases were reported in detail. The first was that of a girl 6 years of age; pyelonephritis, followed by headache, vomiting, frequency of micturition and albuminuric retinitis, developed. The patient died of uremia a few weeks after admission to the hospital. Permission for necropsy was not obtained. In the second case infection of the urinary tract with Escherichia coli and marked

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This paper is an abridgment of a thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Pediatrics.

1. Löhlein, M.: Ueber Schrumpfnieren, Beitr. z. path. Anat. u. z. allg. Path. **63**:570-632, 1916-1917.

2. Quinby, W. C.: A Case of Marked Hypertension in a Boy of Fourteen Associated with Congenital Hydronephrosis and Nephritis, Boston M. & S. J. **189**:485-486 (Oct. 11) 1923.

3. Butler, A. M.: Chronic Pyelonephritis and Arterial Hypertension, J. Clin. Investigation **16**:889-897 (Nov.) 1937.

elevation of blood pressure were present. This patient was removed from the hospital against advice, which prevented further study. The third case was that of a boy 7 years of age who had symptoms of hypertension for several years. Retinal vascular changes were present, and the blood pressure was 240 systolic and 190 diastolic. Necropsy revealed cardiac hypertrophy and dilatation, sclerosis of the aorta and the coronary and cerebral vessels, bilateral pyelonephritis and hydronephrosis. The fourth case was that of a boy 11 years of age who had bilateral pyelonephritis, hypertension and cardiac failure. Necropsy revealed bilateral chronic pyelonephritis and renal arteriosclerosis. The fifth patient was a boy 7 years of age; in this case hypertension and cardiac failure developed nine months after the removal of a renal calculus from the right kidney. After nephrectomy the blood pressure returned to normal and had remained so for twenty months at the time the report was written. This apparently is the first reported case in which nephrectomy was performed for the express purpose of lowering the blood pressure.

Barney and Suby [4] reported the case of a girl 10 years of age who had a history of pyelonephritis of three years' duration. The blood pressure varied from 185 to 200 mm. systolic and from 130 to 170 mm. diastolic. A urogram revealed unilateral renal involvement. Twenty-four hours after nephrectomy the blood pressure was 110 mm. systolic and 70 diastolic. Twenty-one months later it was 98 mm. systolic and 60 diastolic.

Weiss and Parker [5] reported a large series of cases. In 1 case, that of a girl 12 years of age, the sequence of events was pyelonephritis, hypertension and death because of circulatory collapse. At necropsy an atrophic, pyelonephritic left kidney was found, without evidence of pyelonephritis in the right kidney. Examination of the pyelonephritic kidney disclosed an advanced degree of arteriolosclerosis; the vascular changes in the right kidney were similar but less severe.

Similar cases of children have been reported by Bothe [6]; Kennedy, Barker and Walters [7]; Nesbit and Ratliff,[8] and Smith, Weiss, Lillie,

4. Barney, J. D., and Suby, H. I.: Unilateral Renal Disease with Arterial Hypertension: Report of a Case Apparently Cured Following Nephrectomy, New England J. Med. **220**:744-746 (May 4) 1939.

5. Weiss, S., and Parker, F., Jr.: Pyelonephritis: Its Relation to Vascular Lesions and to Arterial Hypertension, Medicine **18**:221-315 (Sept.) 1939.

6. Bothe, A. E.: Pyelonephritis in Children and Adults with Hypertension, J. Urol. **42**:969-981 (Dec.) 1939.

7. Kennedy, R. L. J.; Barker, N. W., and Walters, W.: Malignant Hypertension in Child: Cure Following Nephrectomy, Am. J. Dis. Child. **61**:128-134 (Jan.) 1941.

8. Nesbit, R. M., and Ratliff, R. K.: Hypertension Associated with Unilateral Nephropathy, J. Urol. **43**:427-447 (March) 1940.

Konzelmann and Gault.[9] In 1 of Bothe's cases, that of a boy 3 years of age, the blood pressure was elevated to 174 mm. systolic and 120 mm. diastolic; eleven days after dilation of a constriction at the lower end of the left ureter the blood pressure fell to 140 mm. systolic and 95 mm. diastolic.

EXPERIMENTAL AND CLINICAL DATA IN REGARD TO HYPERTENSION AND RENAL ISCHEMIA

The constancy of the vascular changes in the cases reported in the literature gives rise to the question of whether arteriolar thickening and narrowing are secondary to pyelonephritis and whether it produces an obstruction to normal blood flow within the kidney resulting in ischemia which, in turn, may lead to hypertension.

It has been demonstrated that in the dog,[10] monkey [11] and rabbit [12] constriction of the main renal artery of one kidney results in an elevation of blood pressure which may persist for weeks or months but usually is followed by a return of the blood pressure to a lower or the original level within one month. Adequate constriction of both renal arteries results in persistent hypertension. In some of the dogs which had both renal arteries clamped the blood pressure after a time tended to return to a lower level. Increasing the degree of constriction usually resulted in reelevation of the blood pressure. These results strongly indicate that hypertension is due to diminished blood flow through the kidney. Apparently hypertension is a specific effect of renal ischemia, since ischemia of other organs does not produce it.[13]

Leadbetter and Burkland [14] reported the case of a boy 5½ years of age whose blood pressure was known to have been 170 mm. systolic and 110 mm. diastolic when he was 3 years old. No contrast medium was excreted by the right kidney, according to an excretory urogram.

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9. Smith, L. W.; Weiss, E.; Lillie, W. I.; Konzelmann, F. W., and Gault, E. S.: Cardiovascular-Renal Disease: A Clinicopathologic Correlation Study Emphasizing the Importance of Ophthalmoscopy, New York, D. Appleton-Century Company, Inc., 1940, p. 158.

10. Goldblatt, H.; Gross, J., and Hanzal, R. F.: Studies on Experimental Hypertension: II. The Effect of Resection of Splanchnic Nerves on Experimental Renal Hypertension, J. Exper. Med. **65**:233-241 (Feb.) 1937.

11. Goldblatt, H.: Studies on Experimental Hypertension: V. The Pathogenesis of Experimental Hypertension Due to Renal Ischemia, Ann. Int. Med. **11**:69-103 (July) 1937.

12. Drury, D. R.: The Production by a New Method of Renal Insufficiency and Hypertension in the Rabbit, J. Exper. Med. **68**:693-701 (Nov.) 1938.

13. Goldblatt, H.: Experimental Hypertension Induced by Renal Ischemia: Harvey Lecture, Bull. New York Acad. Med. **14**:523-553 (Sept.) 1938.

14. Leadbetter, W. F., and Burkland, C. E.: Hypertension in Unilateral Renal Disease, J. Urol. **39**:611-626 (May) 1938.

A retrograde urogram revealed an ectopic right kidney located in the pelvis. This ectopic, nonfunctioning kidney was removed. Examination of the renal artery disclosed that it was almost entirely occluded by a mass of smooth muscle. After operation the blood pressure was lowered and remained within normal limits. The removed kidney itself was essentially normal.

Hypertension was produced in Goldblatt's animals without impairment of the excretory ability of the kidneys and with a normal urea clearance and a normal nonprotein nitrogen content of the blood. Goldblatt was able to produce at will either chronic benign or malignant hypertension by adjusting the degree to which the renal arteries were constricted.[15]

Various experiments [16] seem to offer conclusive evidence that hypertension produced experimentally is not the result of a nervous reflex mechanism. Since the nervous reflex mechanism seems to be excluded, various investigators have considered some humoral agent, a so-called pressor substance, to be the cause of hypertension. Much experimental work has been reported recently which favors the view that the ischemic kidney itself produces a pressor substance. Hypertension failed to develop when both renal veins were occluded at the same time that the main renal arteries were constricted, presumably because there was interference with entrance of the hypothetic chemical substance into the blood stream. If the main renal artery of one kidney is constricted and the ischemic kidney is removed some time later when the blood pressure is still elevated, the blood pressure falls promptly to a normal level. Bilateral nephrectomy is not followed by the development of persistent hypertension.[17]

Fasciolo, Houssay and Taquini [16b] carried out perfusion experiments on toads. Their experiments disclosed that the plasma of the venous blood coming from the ischemic kidney produced intense vasoconstriction, which began immediately, increased for several minutes and then

15. Goldblatt, H.: Studies on Experimental Hypertension: III. The Production of Persistent Hypertension in Monkeys (Macaque) by Renal Ischemia, J. Exper. Med. **65**:671-675 (May) 1937.

16. (*a*) Blalock, A., and Levy, S. E.: Studies on the Etiology of Renal Hypertension, Ann. Surg. **106**:826-847 (Nov.) 1937. (*b*) Fasciolo, J. C.; Houssay, B. A., and Taquini, A. C.: The Blood-Pressure Raising Secretion of the Ischaemic Kidney, J. Physiol. **94**:281-293 (Dec. 14) 1938. (*c*) Glenn, F.; Child, C. G., and Heuer, G. J.: Production of Hypertension by Constricting the Artery of a Single Transplanted Kidney, Ann. Surg. **106**:848-856 (Nov.) 1937. (*d*) Page, I. H.: The Relationship of the Extrinsic Renal Nerves to the Origin of Experimental Hypertension, Am. J. Physiol. **112**:166-171 (May) 1935.

17. Goldblatt, H.: Studies on Experimental Hypertension: VII. The Production of the Malignant Phase of Hypertension, J. Exper. Med. **67**:809-826 (May) 1938.

remained stationary. They further demonstrated that plasma of venous blood from normal kidneys produced little or no vasoconstriction.

Page [18] was able to produce persistent hypertension in dogs by placing cellophane around the kidneys. He presented evidence that two factors were concerned in the production of this hypertension, namely, renin, furnished by the kidneys, and an activator in the plasma.

Prinzmetal, Friedman and Abramson [19] demonstrated that saline extracts of ischemic kidneys from dogs with experimental hypertension attributable to unilateral constriction of the renal artery produced greater pressor or less depressor effects than those of the opposite, nonischemic kidney. They also found that the mean pressor effect of saline extracts of the kidneys of 21 patients who had hypertension of various types was greater than that of extracts of the kidneys of 24 subjects who had normal blood pressure.

Goldblatt [17] pointed out that the reports concerning the pressor effect of extracts of ischemic kidneys from dogs with experimental hypertension and of kidneys from patients who had hypertension should be interpreted with caution, because a pressor effect also has been obtained with extracts of normal kidneys [20] and with extracts of various other normal organs.[21] Furthermore, despite the experimental evidence pointing to the formation of a pressor substance by the ischemic kidney, this pressor substance has never been demonstrated in the blood of a patient with hypertension, nor has it been demonstrated in the systemic blood of the Goldblatt dogs.

Pickering [22] found that the changes in arterial blood pressure of anemic patients produced by the transfusion of blood from a patient with essential hypertension are small and are no greater than those produced by the transfusion of an equal volume of blood from a normal donor. Likewise, Collins and Hoffbauer [23] obtained negative results when they gave massive transfusions from large dogs with experimental

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21. Collip, J. B.: A Non-Specific Pressor Principle Derived from a Variety of Tissues, J. Physiol. **66**:416-430 (Dec. 20) 1928.

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renal hypertension to small normal dogs. In some cases relatively enormous amounts of blood were given, as much as 20 per cent of the body weight of the recipient.

MATERIAL

The records of the cases of 510 infants and children, all of whom had pyogenic renal disease and who varied in age from a few months to 15 years, were reviewed. In 91 evidence of pathologic processes was demonstrated by urographic examination, by necropsy or by examination of a removed kidney. This group was selected for further study in order to determine in how many cases an elevation of blood pressure was present, either at the time of the first examination or subsequently; whether impairment of renal function, in so far as this was evidenced by an elevated level of urea in the blood, was correlated with the presence of hypertension, and what was the nature and extent of the pathologic changes in the kidneys which were available for examination. The cases were divided into three groups as follows: Group 1 consisted of cases of unilateral renal lesions in which nephrectomy was performed, group 2 of cases of unilateral renal lesions in which nephrectomy was not performed and group 3 of cases in which the renal lesions were bilateral.

The determination of what constitutes hypertension is less simple in the case of children than in the case of adults. Recognized standards for the limits of normal variation are not available for the different age periods of childhood. Judson and Nicholson [24] and Faber and James [25] have compiled tables in which the average normal blood pressures for each year up to 15 are presented, but since these tables give only average values it is difficult to determine with any degree of accuracy what the limits of normal blood pressure are.

It was decided to consider that the blood pressure was not elevated abnormally if it was less than the arbitrary limit of 120 mm. of mercury systolic and 80 mm. diastolic, regardless of age, even though the average normal levels for the younger children, according to the tables just referred to, are considerably lower than this. Pressures which ranged from 120 to 140 mm. systolic and from 80 to 90 mm. diastolic were regarded as questionably elevated, while those of more than 140 mm. systolic or 90 mm. diastolic were considered elevated.

CASES OF UNILATERAL RENAL LESIONS IN WHICH NEPHRECTOMY WAS PERFORMED (GROUP 1)

This group consisted of 33 cases. The blood pressure was known in 27 cases prior to operation; in 25 the preoperative blood pressure must be considered normal, and these cases will not be discussed in detail except that certain features in regard to the pathologic changes in the removed kidneys will be pointed out. One of the 2 remaining cases (case 1) falls in the doubtful group.

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24. Judson, C. F., and Nicholson, P.: Blood-Pressure in Normal Children, Am. J. Dis. Child. **8**:257-269 (Oct.) 1914.

25. Faber, H. K., and James, C. A.: The Range and Distribution of Blood Pressures in Normal Children: Clinical Application of Statistical Methods to the Interpretation of Deviation from the Normal Average, Am. J. Dis. Child. **22**:7-28 (July) 1921.

CASE 1.—A girl 14 years of age had had attacks of abdominal pain on the left side at intervals of from two to six weeks for seven years prior to registration at the Mayo Clinic. These attacks were associated with fever of several hours' duration and the passage of cloudy urine for a few days thereafter. Hematuria, frequency of micturition and dysuria were absent. The blood pressure on admission was 138 systolic and 88 diastolic, measured in millimeters of mercury. The results of examination of the ocular fundi were negative. Pyuria, graded 2 to 4 on a basis of 1 to 4, and in some specimens albuminuria, graded 1, were present; erythrocytes were not found in the urine. Culture of the urine revealed countless colonies of gram-negative bacilli. An excretory urogram revealed a normal right kidney; the left kidney was poorly filled; its pelvis was dilated and the calices were not visualized. Unfortunately, there were no further preoperative determinations of the blood pressure in this case. Left nephrectomy was performed. Four years later the blood pressure was 110 systolic and 60 diastolic. At this time the patient was in good health and did not have any symptoms referable to the kidneys; examination of the urine gave negative results.

The removed kidney weighed 80 Gm. (normal average weight, 100 Gm.). There was a marked degree of hydronephrosis. Microscopic examination revealed a few hyalinized glomeruli, although most of them were normal. Leukocytic infiltration was widespread, with many lymph follicles present. The arterioles showed thickening and narrowing, graded 2 plus. The tubules showed a moderate degree of atrophy, and many contained colloid casts.

CASE 2.—This case has been reported previously by Kennedy, Barker and Walters. A girl 7 years of age had complained of severe headache for nine months and blurred vision for one month prior to registration at the clinic. For five weeks prior to admission her mother had noted right internal strabismus. The retinal arteries were attenuated; hemorrhagic retinitis and bilateral papilledema, with an elevation of 5 to 6 D., were present. The blood pressure before operation varied from 170 to 210 mm. systolic and from 140 to 166 mm. diastolic. The average preoperative pressure was about 200 mm. systolic and 140 mm. diastolic. The value for urea was 18 mg. per hundred cubic centimeters of whole blood. Pyuria, graded 1, and albuminuria, graded 1 to 2, were present. The excretion of phenolsulfonphthalein was normal. The specific gravity of the urine varied from 1.008 to 1.026. The results of an excretory urographic examination were indeterminate. A retrograde urogram revealed a normal right kidney; the left kidney was small, with abbreviated, clubbed, cicatricial calices which were suggestive of chronic atrophic pyelonephritis.

After nephrectomy the blood pressure fell gradually, and on the sixth postoperative day it was 130 mm. systolic and 104 mm. diastolic. Three weeks after operation there was no evidence of weakness of the right external rectus muscle. Three months after nephrectomy the blood pressure ranged from 102 to 122 mm. systolic and from 70 to 84 mm. diastolic. Seven months after nephrectomy the blood pressure was 104 mm. systolic and 74 mm. diastolic.

The removed kidney weighed only 9 Gm. (normal average weight, about 69 Gm.). There was slight dilatation of the pelvis and calices. At operation a small blood vessel was found to cross the ureteropelvic juncture, and it was believed responsible for the hydronephrosis. Microscopic examination showed that 95 per cent of the glomeruli were hyalinized. Marked leukocytic infiltration and widespread scarring had replaced much of the renal parenchyma. Most of the tubules were atrophic, and many contained colloid casts. The thickening and narrowing of the arterioles was graded 3. Some of the arterioles were obliterated completely.

Pathologic Changes in the Removed Kidneys.—Twenty-seven of the 33 pyelonephritic kidneys removed at operation showed hydronephrosis. Calculi were present in 6. Arteriolosclerosis was observed in many of the specimens; in 18 it was graded 1 or more. In 15 cases little or no arteriolosclerosis was present. In only 4 cases was arteriolosclerosis demonstrated which was graded 2 or 2 plus; in 1 of these cases (case 1) the presence of hypertension was doubtful. The only case in which arteriolosclerosis was graded more than 2 plus was case 2, in which hypertension was marked.

The arteriolosclerotic changes were of the hyperplastic type, consisting for the most part in concentric proliferation of the media which resulted in thickening and narrowing. Little evidence of intimal thickening was noted. Deposition of hyalin was not observed in the arterioles in any of these specimens.

Further microscopic examination revealed varying degrees of leukocytic infiltration, scar tissue, atrophy or dilatation of the tubules and hyalinization of the glomeruli. The tubules in a majority of cases contained colloid casts, but these were not invariably present. There was no correlation between the number of hyalinized glomeruli or the degree of replacement of renal parenchyma by scar tissue and the presence of hypertension. In several cases examination of the kidneys disclosed almost complete destruction of the glomeruli, with widespread formation of scar, but the blood pressure was normal.

Two of the removed kidneys were atrophic, and their weights were less than one sixth of the normal average for the corresponding ages. One of these kidneys was encountered in case 2 and was associated with marked hypertension before operation and with normal blood pressure after nephrectomy. In the other case in which an atrophic kidney was present the blood pressure was normal. Arteriolosclerosis in case 2, in which hypertension was present, was graded 3, and in the case in which the blood pressure was normal it was graded 2.

Follow-up Studies.—Follow-up studies were carried out to determine the levels of blood pressure several years after nephrectomy. Twenty patients were traced, and the blood pressure of all of them was found to be normal. The duration of the follow-up study was from one to sixteen years, the average time being five years after operation.

CASES OF UNILATERAL PYELONEPHRITIS WITHOUT NEPHRECTOMY (GROUP 2)

In 29 of the 35 cases of group 2 in which unilateral pyelonephritis was present but nephrectomy was not performed the blood pressure was recorded. In 4, or 13.8 per cent, of these definite hypertension was present; these 4 cases will be mentioned in detail in subsequent paragraphs. In addition, in 4 cases the blood pressure was somewhat higher

than the average level for the corresponding ages but not sufficiently high for a diagnosis of hypertension to be made. Data for these 4 doubtful cases (cases 3, 4, 5 and 6) are summarized in table 1.

Recorded in table 1 also are the early and late levels of blood pressure, the results of examination of the urine, the levels of urea in the blood and the duration of symptoms or the presence of pyuria without symptoms before the blood pressure was first recorded in the 4 cases (cases 7, 8, 9 and 10) of definite hypertension.

CASE 7.—A girl 11 years of age had her first attack of acute pyelitis at the age af 18 months. Attacks had recurred at intervals of about four months and had been characterized by fever, vomiting and pain in the right lower quadrant of the abdomen. Appendicitis was suspected by the physician in her home locality, and appendectomy was performed a year prior to registration at the clinic. Six months prior to registration her home physician had noted that her blood pressure was 160 mm. systolic and 120 mm. diastolic. The blood pressure on initial examination at the clinic was 160 mm. systolic and 118 mm. diastolic. The retinal arteries showed narrowing, graded 1. Pyuria, graded 1 to 2, and albuminuria, graded 1, were present; the specific gravity of the urine ranged from 1.017 to 1.019; no erythrocytes were present in the urine. The value for urea ranged from 26 to 34 mg. per hundred cubic centimeters of whole blood. Culture of the urine yielded Proteus vulgaris. An excretory urogram revealed a small right kidney with an appearance suggestive of atrophic pyelonephritis and marked diminution in function. The left kidney was essentially normal, except for slight dilatation of the pelvis. Nephrectomy was not performed, since the infection of the urinary tract seemed to be cured after treatment with a ketogenic diet. The patient was examined again three years later, at which time the blood pressure was 148 mm. systolic and 110 diastolic. Examination and cultures of the urine gave negative results. The patient was in good general health and did not have any symptoms referable to hypertension or to the kidneys.

CASE 8.—A boy 11 years of age gave a history of attacks of abdominal pain on the left side associated with nausea and vomiting of from one to two days' duration. These attacks had occurred every few days for a year prior to registration at the clinic. On admission the blood pressure was 148 mm. systolic and 90 mm. diastolic; this same blood pressure level was found whether the readings were taken on the arms or on the left leg. The left kidney was palpable. Pyuria, graded 1 to 2, and albuminuria, graded from a trace to 2, were present; erythrocytes were absent, except after cystoscopic examination; the specific gravity of the urine varied from 1.011 to 1.023. Culture of the urine gave no growth. The values for urea varied from 20 to 26 mg. per hundred cubic centimeters of blood. An excretory urogram revealed a normal right kidney but failed to disclose any contrast medium in the left kidney. Left nephrostomy was performed. Biopsy of the renal pelvis at the time of operation showed evidence of marked chronic pyelitis. The kidney showed hydronephrosis, presumably caused by an anomalous vessel which crossed the ureter at its junction with the pelvis. Two days after operation the blood pressure was 120 mm. systolic and 80 mm. diastolic Several determinations made in the week after operation demonstrated that the blood pressure was constantly at this level. A follow-up study was not carried out, and the present level of blood pressure is not known.

CASE 9.—A girl 14 years of age had had attacks of pyelitis for eighteen months prior to registration at the clinic. Each attack consisted of dysuria, fre-

TABLE 1.—*Summary of Data for the Cases in Group 2 in Which Questionable Elevation of Blood Pressure or Hypertension Was Present*

Case	Age, Years; Sex	Lesion	Average Blood Pressure, Mm. of Mercury: Early Systolic	Early Diastolic	Late Systolic	Late Diastolic	Results of Examination of Urine: Albuminuria, Grade	Pyuria, Grade	Organism on Culture	Erythrocytes, Grade	Urea in Blood, Mg. per 100 Cc.	Duration of Symptoms Before First Blood Pressure Reading, Years
Questionable Elevation of Blood Pressure												
3	12 F	Pyelonephritis; dilatation of ureter	130 (1928)	87	118 (1940)	80	1	2	Esch. coli	Occasional	22	7
4	10 F	Pyelonephritis; hydroureter	130 (1931)	84	112 (1940)	58	1	2	Esch. coli	0	20	8
5	10 F	Pyelonephritis; hydronephrosis	134 (1939)	80	110 (1940)	70	1	1	Esch. coli	1	18	1½
6	8 F	Pyelonephritis; hydronephrosis	110 (1933)	62	140 (1940)	74	1	3	Esch. coli	Occasional	14	5/12
Definite Hypertension												
7*	11 F	Atrophic pyelonephritis	160 (1934)	118	148 (1937)	110	1	2	Proteus vulgaris	0	34	10
8*	11 M	Pyelonephritis; hydronephrosis	148 (1939)	90	After operation 120 (1939)	80	0-2	1-2	No growth	0 to few	26	1
9*	14 F	Atrophic pyelonephritis.	172 (1938)	140	134 (1940)	?	1	1	Esch. coli	0	44	1½
10*	7 F	Atrophic pyelonephritis	220 (1936)	170	Dead (1937)		1-2	1-3	Esch. coli	1	86	7/12

* Reported in detail in text.

quency of micturition and pyuria, which, it is stated, cleared up after a week. Three weeks prior to admission to the clinic the physician in her home locality had noted an elevation of blood pressure, the systolic pressure ranging from 140 to 180 mm. There were no symptoms referable to the kidneys. The patient's only complaint at the time of admission was that she had had several attacks of vertigo during the past month. On admission the blood pressure was 172 mm. systolic and 140 mm. diastolic. Other determinations ranged from 170 to 202 mm. systolic and from 130 to 150 mm. diastolic. Pyuria, graded 1, and in some specimens albuminuria, graded 1, were present; there were no erythrocytes or casts in the urine. The value for urea varied from 22 to 44 mg. per hundred cubic centimeters of blood. The specific gravity of the urine ranged from 1.008 to 1.020. Culture of the urine yielded Esch. coli in colonies too numerous to count. An excretory urogram revealed a small right kidney with reduced function, presumably presenting atrophic pyelonephritis, and a normal left kidney. Nephrectomy was recommended but was refused by the patient's parents. In reply to a follow-up letter nine months later to determine the state of the patient's health and the level of blood pressure it was stated that the local physician had recently dilated the right ureter several times, after which the systolic blood pressure had dropped from about 170 to 134 mm. of mercury.

CASE 10.—A girl 7 years of age had complained of headache for seven months and had had convulsions on two occasions just prior to admission. Frequent determinations of the blood pressure after admission disclosed a level which was consistently higher than 200 mm. of mercury systolic and 170 mm. diastolic. Pyuria, graded 1 to 3, albuminuria, graded 1 to 2, and hematuria, graded 1, were present. The specific gravity of the urine varied from 1.005 to 1.017. The value for urea ranged from 14 to 86 mg. per hundred cubic centimeters of whole blood. Culture of the urine yielded colonies of Esch. coli too numerous to count. Examination of the ocular fundi revealed marked bilateral papilledema, an elevation of 8 D., with severe exudative changes and marked narrowing of the retinal arteries. Bilateral resection of the splanchnic nerve was performed. After the first operation the blood pressure dropped to an average level of 180 mm. systolic and 130 mm. diastolic. There was no appreciable change in the level of blood pressure after the second operation. The patient died at home four months after dismissal from the clinic. Necropsy revealed that the heart was markedly enlarged and weighed 180 Gm. (average normal weight, 100 Gm.). The left ventricle was greatly hypertrophied. The left kidney weighed 100 Gm. (normal average weight, 74 Gm.). The right kidney was atrophic and weighed only 30 Gm. Microscopic examination of the hypertrophied left kidney revealed that it was essentially normal except for the presence of arteriolosclerosis, graded 2. Some of the arterioles showed deposition of hyalin, although the majority revealed concentric hyperplasia of the media without deposition of hyalin. Microscopic examination of the atrophic right kidney disclosed an advanced stage of pyelonephritis. Only a few normal glomeruli remained; nearly all of them were hyalinized. Arteriolosclerosis, graded 3 plus, was present. Many of the arterioles were obliterated completely. Deposition of hyalin was noted in many of the glomeruli.

BILATERAL PYELONEPHRITIS (GROUP 3)

Group 3 consisted of 23 cases. Blood pressure readings were available in 19; in 3, or 15.8 per cent, of these there was a definite elevation of pressure. Data for these cases are summarized in table 2,

TABLE 2.—*Summary of Data for the Cases in Group 3 in Which Questionable Elevation of Blood Pressure or Definite Hypertension Were Present*

Case	Age, Years; Sex	Lesion	Average Blood Pressure, Mm. of Mercury				Results of Examination of Urine				Urea in Blood, Mg. per 100 Cc.	Duration of Symptoms Before First Blood Pressure Reading, Years
			Early		Late		Albuminuria, Grade	Pyuria, Grade	Organism on Culture	Erythrocytes, Grade		
			Systolic	Diastolic	Systolic	Diastolic						
Questionable Elevation of Blood Pressure												
11	10 M	Pyelonephritis; hydronephrosis	(1935) ?	?	(1939) 138	86	2	4	Streptococcus faecalis	1	44	5
12	10 M	Atrophy of left kidney; bilateral pyelonephritis	(1935) 126	88	(1940) 135	80	1	1	Micrococci	0	60	9
13	9 M	Bilateral pyelonephritis	(1937) 138	100	(A few days later) 110	60	2	4	Esch. coli	1	44	5
Definite Hypertension												
14*	14 M	Pyelonephritis	(1934) 126	94	(1940) 140	92	1-2	2-4	Micrococci; Esch. coli	0	36	2
15*	10 M	Right kidney functionless; left kidney, hydronephrosis and pyelonephritis	(1935) 142	104	(1940) 106	72	0-2	1-4	Micrococci	0	26	1/6
16*	9 F	Pyelonephritis	(1938) 230	170	(1939) Dead		1-3	1-3	Esch. coli	Occasional	86	3/4

* Reported in detail in text.

and they will be reported in detail. In addition to the 3 cases in which definite hypertension was an associated condition, 3 other cases in which the blood pressure was somewhat higher than the normal level for the corresponding age are classed as doubtful examples of hypertension. Data for these 3 cases are also summarized in table 2.

CASE 14.—A boy 14 years of age had had diurnal enuresis since birth. The blood pressure on admission was 126 mm. systolic and 94 mm. diastolic. Pyuria, graded 2 to 4, and albuminuria, graded 1 to 2, were present; erythrocytes were absent from the urine, and its specific gravity ranged from 1.007 to 1.018. The value for urea varied from 20 to 60 mg. per hundred cubic centimeters of whole blood; usually, it was approximately 36 mg. Culture of the urine revealed the presence of micrococci and Esch. coli. Roentgenograms of the spinal column and neurologic examination disclosed a deformity of the sacrum. Sensitivity to pain was diminished over the distribution of the fourth and fifth sacral nerves. Urologic examination disclosed that the left kidney had a duplicated type of pelvis, with dilatation of the lower portion of the pelvis and the calices, and that there was slight dilatation of the right renal pelvis. A diagnosis of cord bladder and infection and dilatation of the upper portion of the urinary tract was made. Resection of the presacral nerve was performed in an attempt to relax the sphincter and correct enuresis. The condition of pyelonephritis was resistant to chemotherapy (methenamine and ammonium chloride). The patient was seen again five years later, at which time his blood pressure was 142 mm. systolic and 98 mm. diastolic; pyuria, graded 4, was present, and culture of the urine revealed the presence of Esch. coli. The value for the blood pressure a year later was 140 mm. systolic and 92 mm. diastolic.

CASE 15.—A boy 10 years of age complained of attacks of pain in both lower quadrants of the abdomen and in both costovertebral regions for two months prior to registration. Examination of the urine during this time by the local physician revealed pyuria. Dysuria, frequency of micturition and fever had never been present. The blood pressure on admission was 142 mm. systolic and 104 mm. diastolic. Pyuria, graded 1 to 4, and albuminuria, graded from a trace to 2, were present; only an occasional erythrocyte was seen in the urine prior to operation. Culture of the urine disclosed micrococci in colonies too numerous to count. The value for urea ranged from 22 to 26 mg. per hundred cubic centimeters of whole blood. An excretory urogram disclosed no contrast medium on the right side; a huge hydronephrotic kidney was visualized on the left. An obstruction was found at the neck of the bladder, and suprapubic cystostomy was performed; a few days later sphincterotomy was performed. The systolic blood pressure during the patient's stay in the hospital varied from 130 to 160 mm.; the diastolic pressure remained at about 90 mm. A follow-up letter was sent five years later to determine the level of blood pressure and the general condition of the patient. In the reply it was stated that the blood pressure was 106 systolic and 72 diastolic.

CASE 16.—A girl 9 years of age had complained of severe headache for nine months prior to registration. A week before admission to the clinic she was comatose and had generalized convulsions. On admission the blood pressure was 230 systolic and 170 diastolic. After five days in bed the average pressure was 160 systolic and 120 diastolic. The specific gravity of the urine was fixed between 1.005 and 1.011. Pyuria, graded 1 to 3, albuminuria, graded 1 to 3, and an occasional erythrocyte were present. Culture of the urine yielded Esch. coli in colonies

too numerous to count. The results of examination of the cerebrospinal fluid were negative. The value for urea was 86 mg. per hundred cubic centimeters of whole blood. The excretion of phenolsulfonphthalein was 40 per cent in two hours. Examination of the ocular fundi revealed bilateral papilledema, with an elevation of 4 to 5 D., and hemorrhage and marked narrowing of the retinal arteries. An excretory urographic examination showed poor visualization of the kidneys and ureters, and the results were indeterminate. The patient died at home a little more than a year after dismissal from the clinic. Further data are not available.

CORRELATION BETWEEN LEVEL OF UREA IN BLOOD AND HYPERTENSION

There appears to be no correlation whatever between renal function, in so far as this is evidenced by the level of urea in the blood, and hypertension in this entire series of cases. Of the 8 cases in which there was a definite elevation of blood pressure, in only 2 was the level of urea in the blood definitely elevated; the value for urea in both cases was 86 mg. per hundred cubic centimeters of whole blood, and in both the patient died. On the other hand, in several of the cases in which the blood pressure was normal the value for urea in the blood was markedly elevated, being in some cases as high as 100 mg. per hundred cubic centimeters.

These observations are in agreement with the experience of others who have reported cases of pyelonephritis associated with hypertension, as well as with the results of Goldblatt. He found that when hypertension was induced in experimental animals by renal ischemia the renal function remained normal except when the ischemia was made so severe that malignant hypertension resulted.

COMMENT

From the cases previously reported and those reported in this paper it is evident that hypertension is not a rare symptom in pyelonephritis in children. In 8 of the 75 cases in which the blood pressure determinations were available definite hypertension was present, an incidence of about 10 per cent. In addition, there were 8 cases in which the blood pressure was above the normal average for the corresponding age but was not elevated sufficiently to permit the diagnosis of definite hypertension.

It is worthy of particular note that chronic unilateral pyelonephritis, especially of the atrophic type, may be associated with hypertension, and that in many such cases in which nephrectomy was performed the blood pressure was normal thereafter. Braasch, Walters and Hammer [26] studied the cases of a large series of adults who had had surgical opera-

26. Braasch, W. F.; Walters, W., and Hammer, H. J.: Hypertension and the Surgical Kidney, Proc. Staff Meet., Mayo Clin. **15**:477-478 (July 24) 1940.

tions for various types of renal lesions. These authors stated that it may be predicted that hypertension will be relieved by surgical operation in approximately 70 per cent of the cases in which it accompanies atrophic pyelonephritis, in 50 per cent of the cases in which it is associated with renal tuberculosis and in 25 per cent of the cases in which it accompanies renal stone, hydronephrosis or tumor. They also found that the blood pressure is not always permanently lowered after operation but that it may remain reduced for a year or more and then hypertension may recur.

In 4 of the cases in the series reported herein in which hypertension was present at the time of an earlier admission blood pressure readings were normal or nearly normal at some date after operation.

In each of 3 of the 8 cases of definite hypertension one atrophic kidney was present. In 1 case in which an atrophic kidney was removed at operation the blood pressure was normal before operation.

It should be emphasized that in the majority of cases of hypertension in this series the value for urea in the blood was normal; therefore the hypertension cannot be attributed to impaired renal function in so far as this was evidenced by the level of urea. Further data in regard to the excretion of phenolsulfonphthalein, urea clearance and the results of concentration and dilution tests would have helped to make this observation more conclusive. In 6 of the 8 cases of hypertension the level of urea in the blood was normal; it was elevated in only 2. On the other hand, in several of the cases in which the blood pressure was normal there was marked elevation of the level of urea.

Arteriolosclerosis was present in more than 50 per cent of the 33 pyelonephritic kidneys removed at operation. In 13 cases the degree of arteriolosclerosis was slight, being graded about 1, while in 4 cases it was graded 2. In none of these 17 cases was definite hypertension present. In the only case of definite hypertension in this group (case 2) the arteriolosclerosis was graded 3. Of the 8 cases of definite hypertension, both kidneys were available for study in only case 10. Arteriolosclerosis, graded 3, was present in the atrophic pyelonephritic kidney, while in the opposite, hypertrophied kidney, which was essentially normal otherwise, the arteriolosclerosis was graded 2.

The view that renal ischemia may produce an elevation of blood pressure in experimental animals seems to have been proved conclusively. That this may also be the case in certain human beings with pyelonephritis seems likely from the evidence available, but it has not yet been proved beyond question.

Any one studying this problem wonders why it is that hypertension will develop in only a relatively small percentage of a group of cases of essentially the same type and degree of renal damage. It should be borne in mind that chronic glomerulonephritis is not associated with hypertension in all cases.

CONCLUSIONS

Hypertension associated with chronic pyelonephritis in children is not rare; it was present in about 10 per cent of 75 cases.

Nephrectomy or the relief of obstruction to urinary flow in cases of unilateral pyelonephritis and hypertension frequently is followed by a fall in blood pressure to a normal level.

There is no correlation between the level of urea in the blood and the blood pressure.

Many pyelonephritic kidneys show slight to moderate degrees of arteriolosclerosis in the presence of normal blood pressure.

MYATONIA CONGENITA (OPPENHEIM)

ACCOMPANIED BY CONGENITAL INTRASPINAL TUMOR, DEVELOPMENTAL RETARDATION AND MALFORMATION

F. H. LEWEY, M.D.
PHILADELPHIA

The pathogenesis of myatonia congenita (Oppenheim) is still highly controversial, despite the reports of 32 cases in which necropsy was performed. Spiller,[1] Lereboullet and Baudouin,[2] Councilman and Dunn[3] and Silberberg[4] were unable to find pathologic changes in the nervous system; alterations in their cases were limited to the muscles.

In 26 other cases in which necropsy was performed, reported by nineteen authors, pathologic changes of varying kind and degree were observed in the anterior horn cells, the spinal roots and the muscles. Seven of these authors (Anderson and Reeves,[5] Greenfield and Stern,[6] Grinker,[7] von Lehoczky,[8] Neumann,[9] Slauck[10] and Tuthill and Levy[11])

Read at a meeting of the American Association of Neuropathologists in Atlantic City, N. J., June 9, 1941.

From the Children's Hospital in Philadelphia and the Laboratory of the Neurosurgical Department in the Hospital of the University of Pennsylvania.

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5. Anderson, R. L., and Reeves, D. L.: Amyotonia Congenita: Report of a Case with Autopsy Findings, Bull. Los Angeles Neurol. Soc. **5**:210, 1941.

6. Greenfield, J. G., and Stern, R. C.: The Anatomical Identity of the Hoffmann-Werdnig and Oppenheim Forms of Infantile Muscular Atrophy, Brain **50**:653, 1927.

7. Grinker, R. R.: The Pathology of Amyotonia Congenita: A Discussion of Its Relations to Infantile Progressive Muscle Atrophy, Arch. Neurol. & Psychiat. **18**:982 (Dec.) 1927.

8. von Lehoczky, T.: Ueber die Myatonia congenita Oppenheim und ihre Beziehungen zur Werdnig-Hoffmannschen Krankheit, Arch. f. Psychiat. **71**:491, 1924.

9. Neumann, P.: Zur pathologischen Anatomie der Myatonia congenita, Deutsche Ztschr. f. Nervenh. **71**:95, 1921.

expressed the opinion that progressive degeneration and eventual loss of the anterior horn cells were the primary cause of the disease. Hence, according to this opinion myatonia congenita is a fetal form of the Werdnig-Hoffmann type of infantile progressive spinal muscular atrophy.

Bielschowsky,[12] on the other hand, has expressed the belief that the nerve cell forms observed in his 4 cases cannot be explained on that basis but should be characterized as signs of developmental retardation and malformation. The same holds true, according to the opinion he expressed, for the muscular alterations. Bielschowsky, Archangelsky and Abrikossoff,[13] Brouwer,[14] Collier and Wilson,[15] Foot,[16] Krabbe,[17] Nielsen,[18] Rothmann [19] and Skoog [20] have expressed the belief, therefore, that in myatonia congenita the muscular changes do not follow but parallel the disease of the central nervous system.

The concept of developmental retardation is strengthened by the observation that in some cases of myatonia congenita the posterior columns and the anterior and posterior spinocerebellar tracts were not myelinated or were not completely myelinated at the end of the third month of life; neither was the white matter of the brain in 2 instances (Bielschowsky). The cortical and cerebellar cells and the cortical architecture were involved in 3 cases (Bielschowsky, Concetti [21] and

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10. Slauck, A.: Ueber Myatonia congenita und infantile progressive spinale Muskelatrophie, Deutsche Ztschr. f. Nervenh. **67**:1, 1921.

11. Tuthill, C. R., and Levy, M. G.: Amyotonia: Report of a Case with Histological Observations, Am. J. Dis. Child. **41**:591 (March) 1931.

12. Bielschowsky, M.: Ueber Myatonia Congenita, J. f. Psychol. u. Neurol. **38**:199, 1929.

13. Archangelsky, W., and Abrikossoff A.: Fall von Myatonia congenita (Oppenheim) mit Autopsie, Arch. f. Kinderh. **56**:101, 1911.

14. Brouwer, B.: Amyotonia Congenita (Oppenheim's Disease), in Leerbook der Zenuwsiekten, Haarlem, de Erven F. Bohn, 1930, vol. 2, p. 246.

15. Collier, J., and Wilson, S. A. K.: Amyotonia Congenita, Brain **31**(pt. 1): 1, 1908.

16. Foot, N. C.: Report of a Case of Amyotonia Congenita with Autopsy, Am. J. Dis. Child. **5**:359 (May) 1913.

17. Krabbe, K. H.: Congenital Familial Spinal Muscular Atrophies and Their Relation to Amyotonia Congenita, Brain **43**:166, 1920.

18. Nielsen, J. M.: Myatonia Congenita of Oppenheim: Report of a Unique Case, Am. J. Dis. Child. **35**:82 (Jan.) 1928.

19. Rothmann, M.: Ueber die anatomische Grundlage der Myatonia congenita, Monatschr. f. Psychiat. u. Neurol. (supp.) **25**:161, 1909.

20. Skoog, A. L.: Myatonia congenita. Bericht zweier Fälle in einer Familie, Ztschr. f. d. ges. Neurol. u. Psychiat. **27**:357, 1914.

21. Concetti, L.: Ueber die idiopathische und diffuse Amyotrophie, Klin.-therap. Wchnschr. **7**:1565 and 1613, 1900.

Conel [22]). Finally, dysplasias and malformations outside the nervous system were observed by Marburg [23] and Bielschowsky.

The theory of developmental retardation and malformation in the causation of myatonia congenita is corroborated by the report of 3 new cases.

REPORT OF CASES

CASE 1.—A girl was admitted to the Children's Hospital, Philadelphia, at the age of 11 weeks. She was reported not to have moved her arms since the second day of life. Examination showed that she did not move her extremities. The arms were completely atonic and the legs rigid. The patient was seen in neuro-

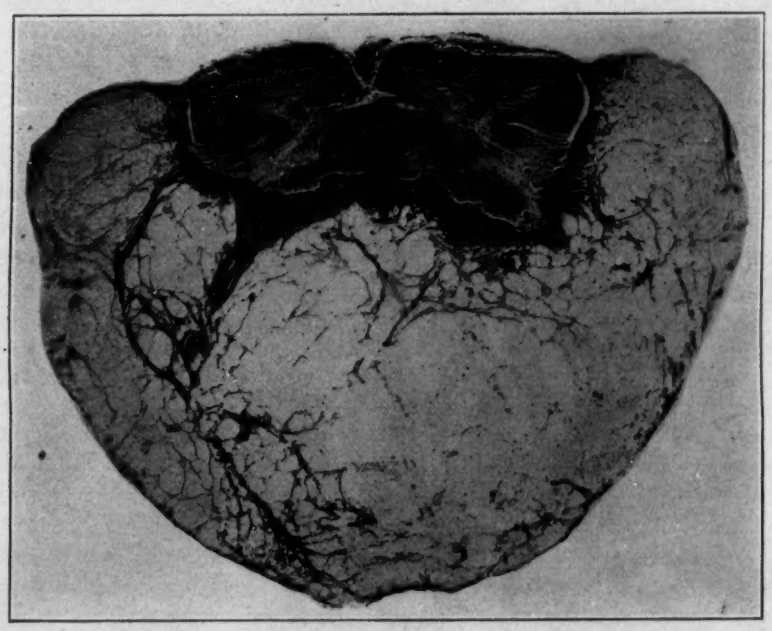

Fig. 1 (case 1).—Cross section through the cervical region of the spinal cord, showing the enormous extramedullary tumor, consisting mainly of fat but also of nerve fibers, which invaded the spinal cord. The tumor was labeled teratoma. Phosphotungstic acid.

logic consultation by Dr. F. H. Leavitt. His impression, and that of the staff of the hospital, was that she suffered from myatonia congenita. The child died on March 3, 1932.

Necropsy (Dr. A. D. Waltz).—Just below the pons there was a slight constriction of the brain stem. In the cervical region of the spinal cord was a grayish oval enlargement, measuring 6 by 2 by 1.5 cm., which appeared to be a firm tumor.

22. Conel, J. L.: Distribution of Affected Nerve Cells in a Case of Amyotonia Congenita, Arch. Neurol. & Psychiat. **40**:337 (Aug.) 1938.

23. Marburg, O.: Zur Klinik und Pathologie der Myatonia congenita, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **19**:133, 1911.

Neuropathologic Changes.—At the posterior side of the spinal cord but surrounding it to a certain degree lay a nonencapsulated tumor, which consisted mainly of fatty tissue. Connective tissue septums permeated the tumor, and cellular parts protruded into the posterior horns. Close to the cord small whorls of arachnoid were included in the connective tissue. Within the tumor mass were nerve fibers which lacked axis-cylinders within their myelin sheaths, while the roots entering the posterior horn contained neurofibrils. The anterior horns showed a number of well preserved large nerve cells and many small cells, a picture not unlike that observed in the 2 other cases of this series. No material and no description are available for the other parts of the spinal cord.

Fig. 2 (case 2).—Cross section of the lumbar portion of the spinal cord. The posterior roots are well myelinated, while the anterior roots are almost devoid of myelin. Myelin is absent from the pyramidal tracts bilaterally. Weil myelin stain.

Summary.—The condition of a baby 11 weeks of age who seemed not to have moved the arms and possibly not the legs since birth was clinically diagnosed as myatonia congenita. Those pathologic changes for which descriptions are available seem to be compatible with this diagnosis. However, in addition a congenital tumor of the cervical portion of the spinal cord was present. It consisted mainly of fat and nerve fibers and was labeled teratoma.

Case 2.—The patient was the parents' third child; the 2 siblings were normal. The intrauterine movements before his birth were active. It is not clear whether the baby moved during the first weeks of life. However, in his sixth week the mother became alarmed because the child did not move his legs, barely moved his arms and was unable to hold up his head or to turn it around.

On admission to the Children's Hospital, Philadelphia, at the age of 2 months, examination by Dr. John P. Scott showed a well nourished baby. The extremities did not move at all and fell by gravity when elevated. There was marked muscular atonia but no muscular atrophy. All of the tendon reflexes were absent. Partial atrophy of the optic nerve was observed (Dr. A. G. Fewell). Roentgen examination of the bones of the legs (Dr. R. S. Bromer) showed "thinning of

Fig. 3 (case 2).—Section of the lumbar portion of the spinal cord. The normal anterior horn cell at the right is in contrast to the small cells in which almost no Nissl substance is visible. Toluidine blue.

the cortex, with a tendency to bone atrophy and secondary decalcification, such as is usually seen in cases of myatonia congenita." A clinical diagnosis of myatonia congenita (Oppenheim) was made. The child died suddenly on Nov. 13, 1940.

Necropsy.—The thymus was large, and there was atelectasis of the upper lobe of the right lung. The muscle fibers of the thigh appeared pale and fatty.

Neuropathologic Changes.—Only the lumbar and sacral portions of the spinal cord were removed. The lumbar portion of the cord showed all of the characteristics of myatonia congenita. The anterior roots were almost unmyelinated, while the posterior roots had normal myelin sheaths (fig. 2). The anterior horns contained only a small number of normal large nerve cells (fig. 3), while the rest of the nerve cells were small and almost devoid of Nissl substance. There was no indication whether these small but mature cells were degenerated large cells, cells that had failed to develop to normal size or simply normal small cells. The glia fiber carpet in the anterior horns was denser than that encountered normally, but it was not dense enough to warrant one's speaking of a scar. The crossed pyramidal tracts were bilaterally unmyelinated.

A section through the sacral portion of the spinal cord, taken about four segments below the section previously described, showed exactly the same condition

Fig. 4 (case 2).—Section of the sacral portion of the spinal cord. There are a duplication of the central canal and an epithelial ependymoma outside and independent of the spinal cord. Phosphotungstic acid.

as that in the lumbar area. However, in addition a typical extramedullary epithelial ependymoma was present (fig. 4).

Summary.—Necropsy in the case of a 3 months old baby who was unable to move the arms, the legs or the head and had complete atonia without muscle atrophy, absence of tendon reflexes and partial atrophy of the optic nerve showed in addition to the lack of large anterior horn cells and absence of myelination of the anterior roots an extramedullary epithelial ependymoma at the level of the sacral portion of the spinal cord.

Case 3.—The patient is the parents' fourth child. The first baby died thirty-six hours after birth; the third is living and well; the second, a boy, was under observation for a long period in the Children's Hospital and the Hospital of Jefferson Medical College, in Philadelphia. None of the neurologic and pediatric

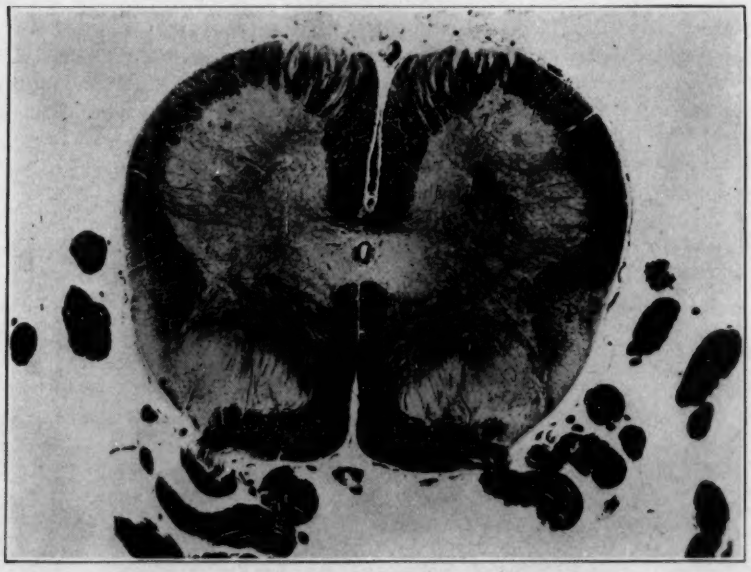

Fig. 5 (case 3).—Cross section through the sacral portion of the spinal cord. The pyramidal tracts (*Py*) are unmyelinated, as are the anterior roots, while the posterior roots are fully myelinated. Weil myelin stain.

Fig. 6 (case 3).—Cross section through the spinal cord in the upper lumbar region. The nerve cells of Clarke's column stand out in contrast to the small number of cells in the anterior and lateral horns. Cresyl violet.

consultants had any doubt that the child suffered from myatonia congenita. Post-mortem examination of the nervous system was not performed.

The patient, who in her mother's opinion had shown more intrauterine activity than the other children, was delivered by cesarian section. When taken home from the hospital, at the age of 6 weeks, she was found to be weak and inactive. This condition increased until admission to the children's ward of the University of Pennsylvania Hospital, on Jan. 3, 1939.

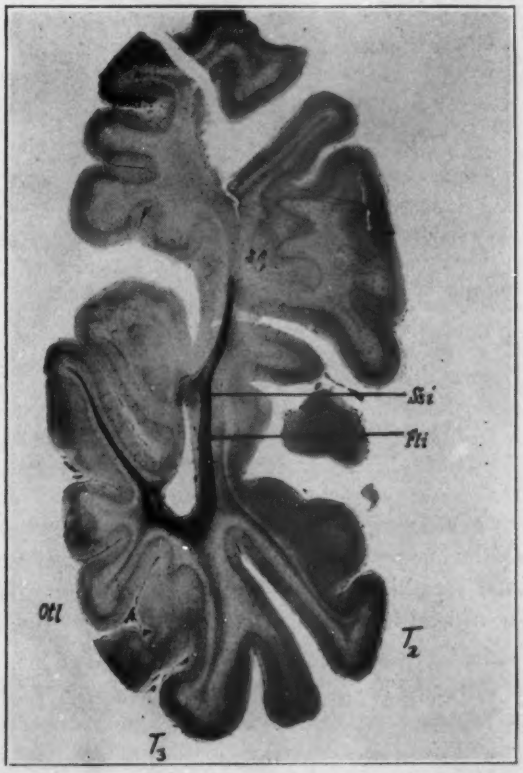

Fig. 7 (case 3).—Cross section through the occipital lobe, showing the presence of cortical cells all over the hemisphere, while the fasciculus longitudinalis inferior (*Fli*) and the stratum sagittale occipitale internum (*Ssi*) are the only tracts fully myelinated. In the medial and inferior portions of the temporal lobe (T_2, T_3) and in the lateral part of the temporo-occipital lobe (*Otl*) a shadow of myelinated fibers is visible. Weil myelin stain.

Examination at that time revealed no movements of the head or the extremities and toneless, flaccid muscles without atrophy. The arms and legs were in some kind of contracture despite the atonia. All of the tendon reflexes were absent. The muscles of the diaphragm and those innervated by the cranial nerves appeared to be the only working muscles. Roentgen examination showed atelectasis of the left lung and bronchoscopic examination an anomalous larynx and bronchial tree. The child died in respiratory distress.

Necropsy.—Postmortem examination showed an adrenal adenoma, a follicular cyst of the left ovary, fetal lobulation of the kidney and lobar pneumonia. The muscles showed patchy areas of degeneration in which the bundles appeared broken and thinned. In sections prepared with the Masson stain not a single muscle bundle stained red as it normally should.

Neuropathologic Changes.—Examination of the central nervous system showed absence of myelin in the crossed pyramidal tracts and anterior roots, while the posterior roots were fully myelinated (fig. 5). The anterior horn cells were very scant, in contrast to those of Clarke's column (fig. 6), and showed various anomalies. In some cells the nucleus was well outlined but no chromatin was present in the cytoplasm and the cell processes were long and pale. In other cells the enlarged nucleus seemed to protrude from the cell. Still other nerve cells were dark and the nucleus pyknotic. Altogether, the anterior horn cells in this case were larger than those in case 2, but very few were of normal size and shape. There was a good deal of glia fiber proliferation in the anterior horns. The observations in the hemispheres were surprising. The cortical nerve cells appeared normal. The axis-cylinders were correspondingly well developed in the white matter, but they were not myelinated, with the exception of those of the fasciculus longitudinalis inferior and the frontopontile and temporopontile tracts (fig. 7).

Summary.—A baby, 11 weeks of age, did not move the head or the extremities; the muscles were atonic despite partial resistance in the arms and legs, the tendon reflexes were absent and there was no muscle atrophy. Necropsy revealed various congenital anomalies. Examination of the central nervous system and the muscles showed the characteristics of myatonia congenita and, in addition, aplasia periaxialis congenita.

COMMENT

The pathologic changes in cases 2 and 3 correspond with those in cases of myatonia congenita reported in the literature. The diagnosis must rest on the clinical features in the first case.

Fourteen of the sixteen authors who have described pathologic conditions in the anterior or lateral horn of the spinal cord have spoken of "severe damage" to its cells, of "reduction in the number" of its cells and of more or less complete "absence" or "degeneration" of the cells. Archangelsky and Abrikossoff, Bielschowsky and Marburg pointed to the fact that the process has to be considered as terminated in their cases. Foot, Krabbe, Marburg, Neumann and Tuthill and Levy found glia proliferation in the anterior horns, indicating scar formation in a region of tissue degeneration, whereas Grinker noted the absence of glia scar formation in his case. Greenfield and Stern, Neumann and Slauck described loss of myelin in the anterior roots secondary to the loss of large anterior horn cells, whereas in the cases of Kaumheimer [24] and Tuthill and Levy the anterior roots were pale in sections prepared with Weigert stain while the anterior horn cells were barely changed. In the

24. Kaumheimer, L.: Zur Klinik und Pathologie der Myatonia congenita, Jahrb. f. Kinderh. (supp.) **78**:170, 1913.

3 cases reported here the number of anterior horn cells was greatly reduced and the anterior roots were barely myelinated. There was a mild to moderate degree of glia fiber proliferation in the anterior horns.

The majority of authors have been noncommittal in labeling the type of changes in the nerve cells and have confined their statements to the observation that very few or no large normal cells were present in the anterior horns. Judging from the cases reported here, not much more can safely be said concerning the nature of the cell loss. Kaumheimer and Tuthill and Levy described the picture of retrograde degeneration of nerve cells, the first, however, mainly in Clarke's column, where this is a normal appearance of the cells, and the latter in the ventrolateral nucleus of the optic thalamus and to a lesser degree in the hypoglossal nucleus. No retrograde changes were seen in the nerve cells in the cases reported here.

There are three possible explanations for the contradictory statements of the authors. The process may be considered as: (1) primary myopathy and neuropathy, with retrograde degeneration of the anterior horn cells; (2) progressive degeneration of the anterior horn cells, with secondary degeneration of the anterior roots and muscles, or (3) deficient development of the large anterior horn cells, the anterior roots and the muscles.

The first suggestion may be discarded. Skoog and von Lehoczky stressed the absence of hypertrophic muscle fibers. Even Anderson and Reeves and Kaumheimer, who reported the observation of hypertrophic muscle fibers, as well as the two authors who described retrograde degenerations in the gray matter of the cord, did not claim the presence of a primary myopathy. Recently, Turner [25] raised again the question whether a true myopathy may occasionally produce the clinical picture of myatonia congenita.

The following two hypotheses are the subject of controversy. The presence of glia proliferation speaks in favor of a postnatal degenerative process in the gray matter. Absence of glia reaction, however, does not exclude progressive degeneration, provided it had terminated before birth. Clinical as well as pathologic considerations speak against the assumption that myatonia congenita is a process analogous to spinal progressive muscular atrophy. In a still progressive or just terminated disease process of previously well developed anterior horn cells and roots one would expect to find muscular fibrillation, electrical reaction of degeneration and muscular atrophy. None of these signs have ever been observed. Likewise, the pathologic equivalents of a progressive disease, such as the presence of scavenger cells or products of degenera-

25. Turner, A. J. W.: The Relationship Between Amyotonia Congenita and Congenital Myopathy, Brain **63**:163, 1940.

tion in the anterior horns, the roots or the peripheral nerves, were always absent.

Mention has been made of Bielschowsky's opinion that the nerve cell forms observed by him and by others cannot be viewed as the result of degeneration and shrinkage of formerly normal cells. He spoke of agenesis and dysplasia of the anterior horn cells with insufficient expansion of their neurons and incomplete development of their motor end plates in the muscles. However, he admitted that there is in addition indication of a still progressive process. Bielschowsky, as well as Tuthill and Levy, described neuroblasts in the brain and the anterior horns of the spinal cord; the former also mentioned the presence of heterotopic nerve cells in the white matter of the cord. No neuroblasts or heterotopic cells were seen in the cases reported here, but abnormal, dysplastic, very small though mature anterior horn cells were observed.

The difference of opinion concerning the alterations in the muscles seems to be more of a quantitative than of a qualitative nature. Spiller and Archangelsky and Abrikossoff clearly expressed the opinion that the muscular changes in their cases represented an "arrest in development." Anderson and Reeves, Conel, Kaumheimer, Krabbe, von Lehoczky, Neumann, Skoog and Slauck described changes in the diameter and the staining quality of the muscle fibers, the presence of degenerating and atrophic fibers mixed with normal fibers, vacuolation of fibers and connective tissue scar formation. Anderson and Reeves, as well as Kaumheimer, in addition observed hypertrophic fibers. Marburg was more impressed by the perifibrillary changes than by changes inside the fibers. Bielschowsky, Foot, Greenfield and Stern and Tuthill and Levy stressed the absence of motor end plates from the pathologic muscle fibers and the occurrence of muscle bundles *"en miniature."* Bielschowsky described such bundles as bands of communicating plasma strands, often with tender longitudinal stripes but without cross striation. No transitional stages were seen between these and normal muscle bundles. No gradual degeneration and no regressive processes have been observed.

The dysgenetic character of the process in the anterior horns and the muscles is corroborated by the presence of anomalies in the configuration and architecture of the cortex, anomalies in the globus pallidus, the cerebellum and the optic thalamus (table 1) and, finally, insufficient myelination in the centrum semiovale and certain long spinal tracts (table 2). The peculiar postural rigidity described in the literature and observed in cases 1 and 3 reported here may be caused by such anomalies. It should be mentioned, however, that lack of myelin in the pyramidal tracts in an infant of 3 months must not be considered as pathologic and that the reports of 5 of the cases for which data are given in table 2

do not give sufficient proof of significant pathologic changes in the long tracts.

Familial occurrence of myatonia congenita (Oppenheim) was found by Krabbe in 6 of 60 cases reported. The twin of the child in 1 case in

TABLE 1.—*Pathologic Changes in the Cortex, the Cerebellum and the Brain Stem in Cases of Myatonia Congenita Reported in the Literature*

Author	Changes
Concetti [21]	Cells in cerebral cortex and cerebellum small and poorly stained
Bielschowsky [12]	Polygyrous type of cortical convolutions. Disturbance of cortical architecture: large lamina II, increased number of granules in layers IV and VI. Numerous Cajal cells in molecular layer and neuroblasts in myelin cones (2 cases)
Conel [22]	Four degenerated cells in anterior central convolution and many in globus pallidus
Tuthill and Levy [11]	Primary irritation and neuronophagia of numerous cells in ventrolateral nucleus of optic thalamus

TABLE 2.—*Degenerative Changes in the White Matter of the Brain and the Spinal Cord in Cases of Myatonia Congenita Reported in the Literature*

Author	Changes
* Rothmann [19]	Demyelination of dorsal spinocerebellar tracts and of anterior tracts between root bundles
* Archangelsky and Abrikossoff [18]	Complete demyelination of ventral spinocerebellar tracts
* Bielschowsky [12]	Insufficient development of white matter of convolutions and centrum semiovale (2 cases)
* Beevor, C. E.: Brain **25**: 85, 1902	Marchi degeneration of posterior columns upward to medulla oblongata (in presence of decreased sensibility)
† Councilman and Dunn [3]	Very slight Marchi degeneration in posterior columns, too little to be noticed in routine examinations
‡ Buzzard, F. E.: Brain **33**: 508, 1911	A few scattered areas of Marchi degeneration. Fibers in posterior columns thinned. No demyelination with Weigert stain
‡ Slauck [10]	More Marchi granules in posterior columns and spinocerebellar tracts than elsewhere in white substance. No demyelination with Weigert stain
‡§Kaumheimer [24]	Increased number of nuclei in posterior columns. Scattered glia rosettes in pyramidal, anterior and spinocerebellar tracts. Increased number of Marchi granules, especially in anterior pyramidal tracts. No demyelination with Weigert stain
§ Tuthill and Levy [11]	Myelin in brain and spinal cord stained well but gave up stain easily

* In these cases the diagnosis seems sound.
† The author himself labeled the observations "practically negative."
‡ In these cases the usual results of nonoptimal treatment with osmic acid are evident. In Buzzard's case there was no staining of the tracts and in the cases of Slauck and Kaumheimer diffuse staining with accentuation in some tracts.
§ In these cases the comments are too vague to permit generalization.

which autopsy was performed (Slauck) was reported by the family not to have moved since birth. Two siblings whose birth preceded that of Foot's patient were paralyzed from birth and died of convulsions at the age of 9 weeks and 6 months respectively. Two siblings of the patient in Bielschowsky's case 4 and the brother of the patient in his case 5 died

a few weeks after birth of "weakness." Four siblings of Marburg's patient died in early infancy.

Necropsy in Marburg's case revealed an open foramen ovale, incomplete closure of the ductus Botalli, embryonal lobulation of the kidneys and incomplete separation of the lobes of the lungs. In Bielschowsky's case autopsy showed incomplete closure of the raphe of the spinal cord and persistence of an embryonal lateral sulcus.

The 3 cases of myatonia congenita reported here, with their manifold congenital malformations and developmental retardations inside and outside the nervous system, fit well into this group.

SUMMARY

Three babies who were reported not to have moved the head and the extremities since birth or shortly thereafter showed severe muscular atonia without atrophy but with loss of the tendon reflexes. The clinical diagnosis of myatonia congenita (Oppenheim) was established.

Examination of the spinal cord showed the changes described as characteristic of this disease; in addition, various signs of developmental retardation and malformation were found in several organs, and in 2 instances congenital extramedullary tumors in the spinal canal and in 1 instance congenital aplastic disease of the cerebral hemispheres and the brain stem were noted.

The observations in these cases are taken as further confirmation of the belief that myatonia congenita (Oppenheim) may occur on the basis of developmental retardation and malformation.

DERMATITIS DUE TO "ANTISEPTIC OILS"

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Six children under 3 months of age have been brought to me by mothers who had used "antiseptic baby oil" on the children's faces since discharge from the maternity ward. The torso and limbs had been bathed in soap and water; the face had been cleaned with nothing but the oil. The infants showed a patchy, erythematovesicular dermatitis, with occasional papules, which was obviously itching; the dermatitis was limited almost entirely to the cheeks and forehead. Omission of the "antiseptic baby oil" and application of bland ointments resulted in complete disappearance of the lesions within a few days. A patch test was carried out by applying small bandages soaked in "antiseptic baby oil", bandages soaked in olive oil and liquid petrolatum serving as controls. The bandages were left in situ for forty-eight hours; on removal the area in contact with the "antiseptic baby oil" showed an erythematous and vesicular lesion, while the control areas were completely clear. Results were practically identical for all 6 children.

Thirty newborn infants, from 2 to 9 days of age, were then tested in the same way, except that the control substances were "salad oil" (presumably mainly cottonseed oil) and liquid petrolatum. Of the 30 infants, only 1 showed the typical erythematovesicular response to the "antiseptic baby oil."

Investigation showed that it was common practice for nurses in charge of newborn infants in hospitals to give the infants thorough rubs all over the body with the "antiseptic baby oil" from one to three times a day and to instruct the mothers on discharge from the hospital to wash the bodies of the infants with soap and water but to continue the oil rubs on the face.

The "antiseptic baby oils" now on the market are manufactured by a fairly large number of drug concerns. The labels on a number of samples state that the oil contains hydroquinone, hydroxyquinoline and chlorobutanol; other labels contain no hint of the ingredients, and none gives a quantitative analysis. Weber,[1] in his exhaustive list of chemicals reported to have produced contact dermatitis, did not mention either hydroxyquinoline or chlorobutanol but stated that hydroquinone had produced reactions on the fingers and mentioned its use in developing

1. Weber, L. F.: External Causes of Dermatitis: Lists of Irritants, Arch. Dermat. & Syph. **35**:129-179 (Jan.) 1937.

solutions in photography. White [2] mentioned hydroquinone as a frequent cause of occupational (contact) dermatitis among persons whose work, for example photography, requires frequent exposure to the substance.

Of interest in this connection is the fact that manufacturers of any compound of animal or vegetable oils which may turn rancid are apt to use hydroquinone as a "stabilizer," or antioxidant. Some years ago certain firms presented preparations containing vitamin A to the Council on Pharmacy and Chemistry of the American Medical Association for approval. The report of the Council [3] read as follows:

"Certain firms . . . have used this drug [hydroquinone] as an antioxidant. . . . The Council held that the available evidence does not indicate that the amount of hydroquinone likely to be ingested with the vitamin-containing oils to which it may be added would be injurious. . . . Attention was called, on the other hand, to the fact that . . . no data are available excluding this possibility following the use of such materials over long periods of time. . . . The Council therefore voted disapproval of the use of hydroquinone as an antioxidant in vitamin preparations. . . ."

A cursory survey of the literature disclosed three recent reports on the toxicity of hydroquinone. Oettel [4] described the acute types of poisoning caused by large quantities of hydroquinone; Heubner [5] commented on the more chronic types of poisoning resulting from the repeated ingestion of small quantities, and Busatto [6] reported a case of fatal poisoning with photographer's developing solution.

The possibility of absorption through the skin of an oily solution of a substance which is actually rubbed into the skin at least once a day over long periods seems very definite. It has been common practice for both obstetricians and pediatricians to prescribe oil baths for the first few years of life. Unfortunately, the nurses in charge of the nurseries have in many instances interpreted this to mean the use of an "antiseptic baby oil," such as those described.

The dermatitis of these infants seems to fulfil the common conception of contact dermatitis, since there was no familial or personal

2. White, C. J.: The Dermatergoses or Occupational Affections of the Skin, ed. 4, London, H. K. Lewis & Co., 1934, p. 294.

3. The Use of Hydroquinone as a "Stabilizing" Agent in Preparations Containing Vitamin A, report of the Council on Pharmacy and Chemistry, J. A. M. A. **109**:1454 (Oct. 30) 1937.

4. Oettel, H.: Die Hydrochinonvergiftung, Arch. f. exper. Path. u. Pharmakol. **183**:319-362, 1936.

5. Heubner, W.: Ueber chronische Vergiftungen, Schweiz. med. Wchnschr. **67**:45-51 (Jan. 16) 1937.

6. Busatto, S.: Tödliche Vergiftung mit einem hydrochinonhaltigen photographischen Entwickler, Deutsche Ztschr. f. d. ges. gerichtl. Med. **31**:285-297, 1939.

history of allergy, the lesions were purely epidermal, the offending substance was an allergen but not an antigen or atopen and a patch test gave positive results.

COMMENT

Why so few newborn children show a positive reaction to a patch test with "antiseptic baby oil" as compared with the greater frequency of positive reactions among infants a few months older is not certain. On theoretic grounds it seems likely that there is a definite period during which sensitivity increases with each inunction, until after a few months sensitivity is manifested by a dermatitis. Such an explanation would be in accord with Straus's [7] observation that although children under 3 years of age are not sensitive to poison ivy they can be made so by sufficient contact. Also, Bloch and Steiner-Wourlisch [8] showed that although most persons living in Switzerland are not naturally hypersensitive to primrose "all of them become sensitive under repeated exposure to it." Daily rubs of the entire body with hydroquinone dissolved in oil may have resulted in the production of hypersensitivity to hydroquinone in the children mentioned although originally, that is, during the newborn period, they were not sensitive to the substance.

CONCLUSION

The lesions resulting from the application of "antiseptic baby oil" in the cases of 6 infants under 3 months of age and 1 of 30 newborn infants acceptably fulfil the criteria listed for contact dermatitis. The offending substance is, in all probability, the hydroquinone used as an antioxidant. This substance is known to have a high index of sensitivity from a dermatologic standpoint and to be toxic on ingestion. The routine use of a substance containing hydroquinone in the case of infants over a long period should be under careful control.

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7. Straus, H. W.: Artificial Sensitization of Infants to Poison Ivy, J. Allergy **2**:137-144 (March) 1931.

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AN APPARATUS FOR DETERMINATION OF VITAL CAPACITY OF INFANTS

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Since infants cannot cooperate, the apparatus shown in figure 1 was devised to determine their vital capacity. It consists of a 5 gallon (22.7 liter) closed container, similar to a milk can, of sufficiently heavy gage metal so that the walls are rigid. A water manometer is connected to measure the pressure within the container, which is connected by heavy walled rubber tubing with a Marriott face mask.[1]

The container is calibrated by pouring measured amounts of water into it. As shown in figure 2, the pressure increases 1 mm. for each 4.8 cc. of water added to the container, or 0.23 mm. per cubic centimeter.

The vital capacity of an infant is measured by placing the face mask quickly and tightly over his mouth and nose at the end of a full inspiration. The maximum of several determinations is taken as the vital capacity. If the infant draws a still deeper inspiration when the face mask is applied, the sum of the positive and negative excursions of the manometer is the final vital capacity. Comparable results have been obtained with infants of similar ages, weights and chest circumferences.

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1. The mask is made from the nipple of a wide mouth (Hygeia) nursing bottle. A sheet of thin rubber tissue (dental dam), 8 by 10 inches (20 by 25 cm.), is perforated in the center by a piece of hot metal or glass tubing of large bore. The hole is stretched and pulled over the nipple and slipped down to the lower rim. A small amount of rubber cement is applied to hold the tissue and nipple together. A strip of adhesive plaster ⅜ inch (1 cm.) wide is applied around the rim of the nipple so as to overlap the rubber tissue and hold it firmly in place. The extreme tip of the nipple is cut off and a short glass tube, ⅜ inch in diameter, inserted. (Marriott, W. M.: Determination of Alveolar Carbon Dioxid Tension by a Simple Method, J. A. M. A. **66**:1594-1596 [May 20] 1916. Howland, J., and Marriott, W. M.: Acidosis Occurring with Diarrhea, Am. J. Dis. Child. **11**: 309-325 [May] 1916.)

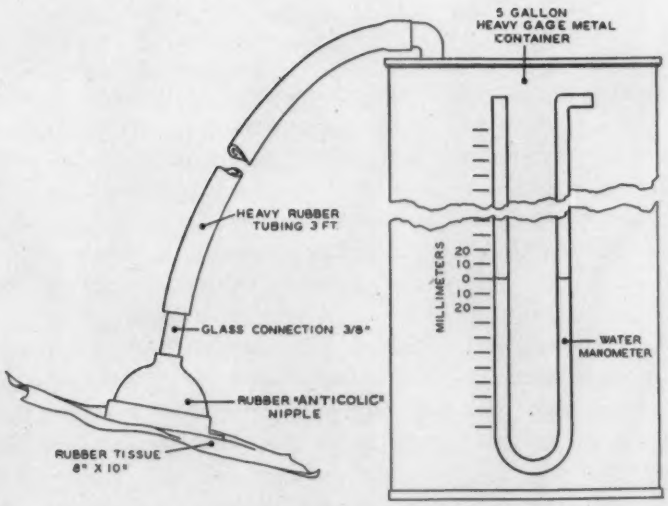

Fig. 1.—Apparatus for the determination of the vital capacity of infants.

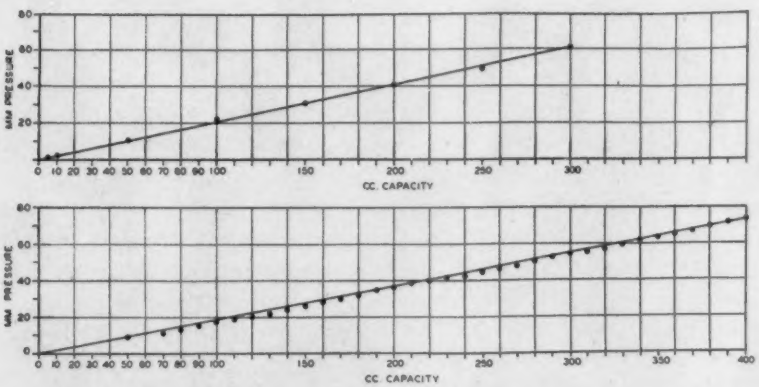

Fig. 2.—Increases in pressure produced by adding measured amounts of water to the container.

THE HYPERACTIVE CHILD

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What is a hyperactive child? When does he become a problem to others? The average child is very active physically, employs useless and exaggerated gestures and finds it difficult to concentrate on one thing for a prolonged period. As he grows he learns to control his motor impulses, becomes less active and more attentive and finally in his teens develops the ability to think before acting and is economical in the expenditure of his physical energy. The extent of normal physical overactivity and the time for the child to become less active vary widely with different children. Annoying as hyperactive behavior may be to parents, fortunately, in most instances, it is regarded as natural, as a phase in the child's development, and not much importance is attached to it. The child whose overactivity results in no particular problems will not be discussed.

There is a type of child who, because of the extent and constancy of his hyperactivity and because of the response of others to his behavior, is considered to present difficulties or problems of management. He is described as restless, wild, impulsive, nervous or fidgety. It is often said of him that "he can't sit still," "must always be doing something," "is aggressive," "always gets into everything and into trouble," "must be watched every minute" or that "he takes all my time." Working with this type of a child in a guidance clinic reveals his constant physical activity, flightiness, pressure of speech and often clumsiness. It is not uncommon in the experience of child guidance workers to find that the hyperactive child is misunderstood by parents, teachers, physicians and social workers. Well adjusted parents may show little concern about the hyperactivity, but great tension, annoyance and counterreaction are displayed by parents who are "on edge" because of their own personal problems. Too often general limitations, based on standards for the average child or on the comfort of adults, are imposed on the hyperactive child in spite of the fact that it may be practically impossible for him to conform. His being different and the way he is treated may lead to new and more serious problems.

By the time the hyperactive child reaches the child guidance clinic it is not the hyperactivity which is the cause of concern, but rather the complaint centers about the results of such behavior—poor school work,

From the Child Center, Catholic University of America.
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difficulty in reading, frequent fighting, failure to adjust in the group, refusal to mind or running away. If the difficulty has not become too serious the parents will say, "the child is not bad, but he just exhausts me and I don't know what to do with him" or "he is so different from other children." Later they begin to believe he is bad, is suffering from a physical disability or is incorrigible.

Hyperactivity is a mode of self expression, a type of conduct that has many components, each effective because of the other. Certain factors are commonly found, and an evaluation of them may help in the understanding of how hyperactivity develops and of the problems resulting therefrom.

All are familiar with the hyperactivity and impulsiveness which may follow an attack of lethargic encephalitis. In cases of other types of hyperkinesis such an organic factor may be present, but it is confusing and often difficult to prove. Timme [1] emphasized the probability of the occurrence of some destructive change in the region about the third ventricle, in the hypophysis and adjacent gray matter, as a consequence of childhood infectious diseases or cerebral trauma during or after birth, which may result in behavior problems of the type being described. The advent of electroencephalography as a diagnostic instrument has caused various investigators [2] employing it in work with children to believe it possible that a basic physiologic disturbance in the brain has been missed in the cases of many children whose disorders were considered primarily psychogenic previous to the introduction of this method of investigation. One should consider such a cause when there is a combination of significant history, typical behavior and certain physical signs. Definite change in development and behavior following trauma to the head, particularly injury accompanied by unconsciousness, or subsequent to an infectious illness, especially one occurring during the first eighteen months of life and associated with high fever, convulsions or stupor, may be significant. Difficult or premature delivery may speak for possible significant birth trauma. If after such illness or trauma the child becomes hyperkinetic, flighty or impulsive or if his behavior is definitely changed out of proportion to the factors in his environmental or emotional life, suspicion should be further aroused. Often there are no definite organic changes. Personality changes rather than neurologic residuals are frequent. However, there may be such significant signs as poor coordination, organic tremors, athetoid movements, marked urge to talk with propulsive features, hyperactive reflexes, polyuria, palsy residuals or disturbance in the endocrine picture.

1. Timme, A. R.: Relationship of Childhood Infections to Behavior, California & West, Med. **49**:1-12 (Dec.) 1938.

2. Jasper, H. H.; Solomon, P., and Bradley, C.: Electroencephalographic Analysis of Behavior Problems, Am. J. Psychiat. **95**:641-658 (Nov.) 1938.

Well meaning and well adjusted parents may find a child with such "organic" hyperactivity trying, and they often struggle with him because of his behavior. The child becomes unusually active and difficult to manage and does not respond as do other children. The parents, not aware of the organic factor involved, may then believe that they have a bad child who refuses to respond to the usual discipline, and so they employ severe measures. As a result of the struggle the child feels unwanted and is badly handled, and these factors may be given all the credit for the child's poor conduct.

Unfortunately, encephalopathy can be a most welcome and a too simple explanation of the undesirable behavior of many children. Probably only a small percentage of children have significant cerebral changes after trauma or childhood infections. The attachment of such an etiologic label makes for a pessimistic attitude in treatment and may lead to an ignoring of the other factors involved. How such a child is managed and the nature of the response to his activity will greatly influence his behavior. Not enough is known at present regarding the results of postencephalitic damage to stress it unduly. Significant histories are indefinite, physical signs are often absent or nonspecific and the behavior can frequently be explained by other factors. An organic explanation of such behavior, on the basis of the pathologic localization of the involved areas, would still be speculative. It appears that connections between the higher and the lower centers are involved, and the reactions of the lower centers are intensified.

The study of hyperactive children who are referred to a child guidance clinic shows that a large number of them are mentally retarded. There is no direct relation between hyperkinesis and mental retardation, but both may arise from a common underlying brain defect. Such conduct of a retarded child may also result either from the failure of the parents to accept him as he is or from his inability to adjust to the average environment. Such a child may find physical activity, which is usually not very purposeful, to be his only mode of expression.

A child may present problems of management as a result of his activity because of unfortunate environmental factors, which generally are not causative but accentuating. A too confining environment, a difficult school situation, a nonunderstanding teacher or a home of discord may sponsor overactivity or make the normally active child a problem hyperactive child. Childers [3] found in his study of such children that their social milieu was disordered and chaotic and that there were frequent changes in the home, inadequate and faulty management and yelling and nagging on the part of the parents.

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3. Childers, A. T.: Hyperactivity in Children Having Behavior Disorders, Am. J. Orthopsychiat. **5**:227-243 (July) 1935.

One of the most important factors, and one which gives a particular significance to the others, is the nature of the child's relationship to others and to his parents in particular. In a child who feels unwanted, rejected or insecure anxiety may develop, with hyperactivity as its physical manifestation. A fearful child is often a hyperactive child. Feelings of inferiority and inadequacy may also make for such behavior and accentunate it once it has been initiated. The conduct of the hyperactive child may create a disturbance so annoying that it calls forth counterreactions and secondary symptoms. Pressure may be expended on the child to be quiet and inactive. Naturally he rebels, only to meet further destructive attitudes on the part of the parents. Thus a vicious cycle is set up, and the parent and child become deadlocked in a struggle.

In the school, as well as in the home, such a child meets with considerable difficulty. Inability to remain quiet in the classroom as do the other students, together with increased distractibility, results in poor work and gives the child the reputation of being a trouble maker. Because of impulsiveness he plays poorly with other children. Although such a child often shows a marked desire to gain attention and to be a leader and a winner in games, because of his conduct he frequently winds up as a poor loser and is regarded as a nuisance. He seeks friends but cannot make them and instead often gets into fights with others in a group. In many cases these secondary symptoms, conduct as a result of hyperactivity, become foremost, and the preceding factors in the child's difficulties are not properly evaluated.

There is a striking similarity in the behavior of all hyperactive children regardless of the cause of the hyperkinesis. The final picture resulting from emotional factors can be practically identical with that following cerebral damage. Such behavior has been said to be of the "postencephalitic type" even though the child may never have had encephalitis. Anderson and Mambar [4] have stated this well.

> This type of behavior, because so characteristic of the post encephalitic has received the name "post encephalitic behavior." It is, however, by no means the result of encephaltis only. Injuries, infectious diseases, endocrine disorders, all may be productive of similar effects. Likewise, prolonged exposure to attitudes and management emotionally of an undesired sort may be provocative of behavior clinically indistinguishable from that so termed. . . . Encephalitis is a sudden and attention-compelling influence; long-continued destructive attitudes are less obvious.

What becomes of the hyperactive child? One does not see many hyperactive adults. Actually it is unusual to see a child beyond puberty with hyperkinetic symptoms. Except in certain cases in which the

4. Anderson, F. N., and Mambar, R.: Post-Encephalitic Behavior, Soc. Work Technique **4**:67 (May-June) 1939.

disorder has an organic cause the hyperactive child quiets down like other children, if he is given the chance. Increasing maturity leads to greater self control. Unfortunately, before this occurs serious problems may have developed because of the reaction of others to his behavior. The resulting emerging personality may be one that finds it difficult to meet life situations, and substitute modes of expression, also typified by lack of inhibition, may develop.

Because there are so many diverse factors involved, it would be extremely difficult to prognosticate about the outcome of the hyperactivity. After making a study of the prognosis of lethargic encephalitis in childhood Healy [5] concluded that the offering of a prognosis is unwarranted and may be dangerous. The outcome cannot be foreseen. In his group of children with postencephalitic disorders hyperkinetic phenomena tended to disappear gradually and diminished greatly in the second decade of life. If it is difficult to make a prognosis in those cases in which the organic component is so outstanding, it is more so in other situations. An important factor in the outcome is the manner in which the parents and others respond to the child's behavior.

To clarify and to illustrate the factors and the problems encountered in working with such a child, it may be helpful to introduce the cases of 4 children who were seen in a child guidance clinic. Although the basic conduct of all of them was the same or at least very similar, the factors involved in each case were different.

CASE 1.—An 8 year old boy was referred to the clinic because of hyperactivity, failure to mind, inability to concentrate and diurnal and nocturnal enuresis. Not being able to manage him, the mother desired a temporary outside placement. The history revealed that the boy had been delivered with difficulty, by forceps, that he constantly cried and was restless throughout infancy and that he had always had jerkings and twitchings in his sleep, which had continued, though they were diminished, up to the time of referral. The child did not enjoy movies and the radio because he was inattentive and restless. Although he was in school for the third year, he was in the second grade, he could not read and he was considered by the school authorities to be a "problem child." A physical examination showed muscular unsteadiness and hyperactive reflexes. Laboratory studies revealed polyuria and a disturbed water balance. The psychologic study showed the boy to be of dull normal intelligence. Because the father was irresponsible and alcoholic the parents had separated when the boy was 4 years old. The home life had always been chaotic since there was disagreement between the mother and the grandmother concerning the boy's discipline; in addition, the mother, who played the role of breadwinner, had very little time for her son because of her work. Most of the time that she spent with him was passed in a struggle to cause him to be less active and to conform to disciplinary measures.

It was believed that the basic factor in this case was defective development of the nervous system due to birth injury, but there were many additional factors within the home life that contributed to the child's conduct.

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5. Healy, W.: Prognosis of Lethargic Encephalitis in Childhood, Arch. Neurol. & Psychiat. **36**:921-930 (Nov.) 1936.

CASE 2.—When the patient was a year old she became ill with measles, and on the second day her temperature rose to 104 F. A severe convulsion developed, followed by a long period of stupor, but no neurologic changes were noted. However, after the illness there was a marked change in the child's behavior. Within a month petit mal attacks occurred at irregular intervals, several in a day, about once every two or three weeks. In her twentieth month the petit mal attacks became almost daily occurrences, and because her conduct was extremely active and seemingly uncontrolled the child was placed in a hospital for a week, where she underwent a complete medical study. Brain defect, congenital or more likely a complication of measles, was considered the etiologic factor in the child's behavior and the cause of her "spells." Administration of phenobarbital was begun, and she was given ½ grain (0.03 Gm.) morning and evening. The parents were aware of the psychologic as well as the physical factors involved, and they tried to be patient and tolerant about the child's behavior. The hyperactivity and uninhibited behavior continued beyond the first half of the third year, even though the petit mal attacks ceased just after the patient was 3½. When the child was 4 she finally quieted down and was able to make a good adjustment.

The ability of the parents to accept the child and her behavior and not to fight her and her conduct helped to make this possible and probably spared her the development of secondary symptoms.

CASE 3.—The patient was referred to the clinic at the age of 6 years. His mother wanted him placed in a foster home or an institution, because of his extreme hyperactivity and destructive behavior. He refused to stay in school, bullied other children, was hostile toward his younger sister, had enuresis and soiled himself. He was beyond the control of either parent and responded to none of the discipline they employed, which included beating, bribing and removal of privileges. Often they tied him in his chair. The mother stated that the only place they could live with him was in the country, where he might run wild. In her estimation he was bad and incorrigible. The physical examination revealed nothing abnormal except marked restlessness, impulsiveness and underdevelopment, and the psychologic examination indicated that the boy had normal intelligence. A study of the family situation revealed that the mother was extremely unhappy in her marriage and that the supposed father was alcoholic. It was later learned that he was not the real father. The child was illegitimate, the mother having become pregnant during a period when she was separated from her husband. The father always punished the mother through the child, who could well be described as rejected and a symbol of something which both parents wished to remove from their lives. The boy's behavior became so disturbing that it was necessary to remove him from his home. He was placed in a children's convalescent home, and although many observers were skeptical about his adjustment to the orderly discipline of such a setting, he lost all his hyperactivity and destructive behavior and was no longer a "problem" child. In the convalescent home he was accepted and understood and was not subject to his parents' destructive attitudes.

CASE 4.—The patient was old enough for problems to have developed as a result of his hyperactivity and the reactions to it. At the age of 12 years, when he was in the sixth grade, he was referred to the clinic because of inadequate school work, poor social behavior, hyperactivity, minor stealing and sexual delinquency. The history revealed that when the mother learned she was pregnant she became emotionally upset and tried to induce an abortion. After he was born she was very protective of him and showered her affection on him. The family life was supposedly good, but the mother was unstable, there was much rivalry

between the patient and his older brother and it was necessary for the family to move frequently because of the father's occupation. From infancy the boy was hyperactive and constantly got into trouble, and because of his uninhibited conduct he was a matter of great concern to his parents. At school he was always considered to be a problem, except for one year when he had an understanding teacher. Because of his behavior he was unable to make friends or to win favorable attention, although he tried hard to gain both. Because the mother as a child was abused sexually on one occasion, she was constantly concerned about her son's not getting into sexual difficulties and tried to protect him from situations in which he might become involved in sexual play. Probably in part because of his mother's attitude, the boy became involved in sexual play with an adult and later drove his mother almost frantic by being caught in similar play with several little girls in the neighborhood.

The boy showed activity of the typical postencephalitic type, but there were no abnormal physical signs and the medical history was noncontributory. He was constantly active, talked continuously, acted silly and was clumsy. He was conscious that he was regarded as a problem and accepted the fact that he was bad. He seemed to be constantly fumbling in an attempt to understand himself and to make an adjustment to others. The mother was emotionally upset and baffled about dealing with him. Therapy to be effective not only would have to help the boy to find himself but would have to aid the mother in developing a healthy relationship toward him.

In considering treatment it is obvious that because hyperactivity in a child is not a specific entity there is no particular therapy or method of meeting his problem. Hyperactivity may be a symptom, a sign of deep-seated needs which should be met. By discussing with parents how they may meet daily specific situations, they may be helped to develop some insight and a proper attitude toward the child. The hyperactive child requires a routine of living which is varied and yet firm. No definite standards of discipline can be employed; instead, one should make the best of the different situations as they arise. Parents who have read books on child rearing and know what a child should do and how he should respond have a particularly difficult time with such a child. Often a hyperactive child is helped by a change of residence from a compact apartment with its necessary restrictions, to a private home with a yard and a neighboring playground. It is advisable that the child's environment be such that he will have a maximum of freedom and a minimum of restrictions. Since the hyperactive child shows exaggerated behavior when he is tired, he should not be allowed to become fatigued; rest periods are valuable. However, some parents ruin the value of a rest period by making it a time of struggle with the child. Music is very helpful in quieting such a child. Good music in the home and participation in rhythm bands are advisable.

Sometimes a hyperactive child who does not respond at home because of the tenseness and negative influences directed toward him by the parents, because of his conduct, reacts favorably away from home in an environment of understanding and acceptance. Parents may become

so wrought up emotionally over the problem of the child's management that separation from him is sought, and it may be constructive. However, living in a foster home or an institution of the corrective or disciplinary type may be more damaging to the child than remaining in his own home. In school too much effort should not be made to have the child behave as do others in the group. Such a child benefits by having an individualized program and an understanding teacher and by being in a small class.

Too often medical treatment is the only therapy offered for the care of the hyperactive child. It is understood that all physical disorders should be properly handled, so that the child may be in optimal physical health. At times and in certain types of cases drugs may be employed for their sedative effect as a supplementary measure. Frequently physicians and parents give a sedative and ignore the destructive attitudes and tension which either bring about or accentuate the problem. This is equivalent to treating anxiety states and disturbing neurotic symptoms with bromides and doing nothing further. The use of drugs in conjunction with other measures may help the child to become less active and thus allow him to live in a better relationship with those about him. It may be a means of temporarily breaking the destructive vicious cycle related to his problems, so that other measures may be effective. In some cases phenobarbital given morning and evening, has been effective, while in others it has resulted in exaggerated behavior. Timme [1] found helpful in many cases the use of small doses of phenobarbital and massive doses of whole pituitary to produce sedation of the autonomic centers and stimulate the pituitary. Amphetamine (benzedrine) sulfate has proved beneficial [6] for some hyperactive children, on whom it may have the effect expected of a sedative. In particular, school work is often improved. Amphetamine occasionally appears to stimulate a child to increased activity or to make him markedly depressed; its use is contraindicated in such cases.

The main object in the treatment of the hyperactive child should be to help relieve the unfavorable tension in the relationship between child and parent. Then the parents will be able to accept the child as he is, and only then may other treatment measures be effective. Child and parent will be working together toward a common goal instead of struggling over their problems. Favorable changes may then occur in the child's condition. In general this is also true in regard to other behavior problems presented by children.

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6. Bradley, D., and Bowen, M.: Amphetamine (Benzedrine) Therapy of Children's Behavior Disorders, Am. J. Orthopsychiat. **11**:92-103 (Jan.) 1941. Cutts, K. K., and Jasper, H. H.: Effect of Benzedrine Sulfate and Phenobarbital on Behavior Problem Children with Abnormal Electroencephalograms, Arch. Neurol. & Psychiat. **41**:1138-1145 (June) 1939.

Case Reports

RENAL HYPERPARATHYROIDISM WITH CALCIFICATION OF THE ARTERIES IN INFANCY

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Since Mandl's dramatic demonstration [1] that osteitis fibrosa can be relieved by the removal of a parathyroid adenoma, an extensive literature has appeared on hyperparathyroidism. The concept that in some cases hypertrophy of the parathyroid glands and osteitis fibrosa are secondary to chronic renal insufficiency is well established.[2] The close similarity between adult renal hyperparathyroidism and the renal rickets of late childhood and adolescence has been appreciated more recently.[3] Both diseases are characterized by prolonged severe renal insufficiency, altera-

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1. Mandl, F.: Therapeutischer Versuch bei einem Falle von Ostitis fibrosa generalisata mittels Extirpation eines Epithelkörperchentumors, Zentralbl. f. Chir. **53**:260, 1926.

2. (*a*) Literature cited by Anderson, W. A. D.: Hyperparathyroidism and Renal Disease, Arch. Path. **27**:753 (April) 1939. (*b*) Albright, F.; Drake, T. G., and Sulkowitch, H. W.: Renal Osteitis Fibrosa Cystica: Report of a Case with Discussion of Metabolic Aspects, Bull. Johns Hopkins Hosp. **60**:377, 1937. (*c*) Pappenheimer, A. M., and Wilens, S. L.: Enlargement of the Parathyroid Glands in Renal Disease, Am. J. Path. **11**:73, 1935. (*d*) Gilmour, J. R., and Martin, W. J.: The Weight of the Parathyroid Glands, J. Path. & Bact. **44**:431, 1937. (*e*) Castleman, B., and Mallory, T. B.: Parathyroid Hyperplasia in Chronic Renal Insufficiency, Am. J. Path. **13**:553, 1937.

3. (*a*) Hubbard, R. S., and Wentworth, J. A.: Case of Metastatic Calcification Associated with Chronic Nephritis and Hyperplasia of Parathyroids, Proc. Soc. Exper. Biol. & Med. **18**:307, 1920. (*b*) Langmead, F. S., and Orr, J. W.: Renal Rickets Associated with Parathyroid Hyperplasia, Arch. Dis. Childhood **8**:265, 1933. (*c*) Smyth, F. S., and Goldman, L.: Renal Rickets with Metastatic Calcification and Parathyroid Dysfunction, Am. J. Dis. Child. **48**:596 (Sept.) 1934. (*d*) Shelling, D., and Remson, D.: Renal Rickets: Report of a Case Showing Four Enlarged Parathyroids and Evidence of Parathyroid Hypersecretion, Bull. Johns Hopkins Hosp. **57**:158, 1935. (*e*) Price, N. L., and Davie, T. B.: Renal Rickets, Brit. J. Surg. **24**:548, 1937. (*f*) Howard, T. L.: Renal Rickets or Renal Dwarfism, Am. J. Surg. **40**:323, 1938. (*g*) Park, E. A., and Eliot, M. M.: Renal Hyperparathyroidism with Osteoporosis (Osteitis) Fibrosa Cystica, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1937, vol. 3, chap. 29.

tions in the calcium and phosphorus content of the blood and an increase in the urinary excretion of both substances, hypertrophy of the parathyroid glands, metastatic calcification and abnormalities in the bones. Renal rickets differs from adult renal hyperparathyroidism in the age at which it occurs, the fact that the renal insufficiency is usually due to a congenital anomaly and the greater variation in the appearance of the osseous lesions.

No record has been found of the recognition of renal rickets during the first year of life. Several years ago, however, we were able to study an infant who at first presented the picture of hypocalcemic tetany which was somewhat resistant to therapy. When the child was 2 months old a widespread calcification of the peripheral arteries was discovered. This increased progressively until the death of the infant, at the age of 6½ months, due to an infarct of the heart, which resulted from calcification of the coronary arteries. The postmortem observations were characteristic of renal hyperparathyroidism. Soon after this a similar case appeared; because of our first experience the efforts to combat the hypocalcemia were more conservative. Postmortem examination revealed changes similar to those in the first case except for a lesser degree of metastatic and arterial calcification. These 2 cases form the basis of our report.

Since our realization of this syndrome 2 further cases have been recognized clinically, and 1 case, that of a child aged 14 months at death, has been discovered in the autopsy files of the Babies Hospital. These cases are not included in the report because complete data and adequate space are lacking. Reports of 4 further cases of medial calcification of the arteries in infancy associated with severe renal insufficiency have been found in the literature. In none of these reports did the author relate the renal and arterial lesions or describe the bones. Surbek [4] described an infant aged 3 days; in Oppenheimer's second case [5] the child was 4 months old and in her first case 6 months old, and the patient of Bryant and White [6] was aged 7 months. The infant described by Surbek was so young as to raise the question of the significance of renal

4. Surbek, K.: Ueber einen Fall von kongenitaler Verkalkung, mit vorwiegender Beteiligung der Arterien, Zentralbl. f. allg. Path. u. path. Anat. **28**:25, 1917.

5. Oppenheimer, E. H.: Partial Atresia of the Main Branches of the Pulmonary Artery Occurring in Infancy and Accompanied by Calcification of the Pulmonary Artery and Aorta, Bull. Johns Hopkins Hosp. **63**:261, 1938.

6. Bryant, J. H., and White, W. H.: A Case of Calcification of the Arteries and Obliterative Endarteritis Associated with Hydronephrosis in a Child Six Months of Age, Guy's Hosp. Rep. **55**:17, 1901.

excretion in utero. The vascular lesions all appear to be identical with those in our first case. Medial calcification of the arteries in infancy is not confined to the cases of renal hyperparathyroidism, however, as evidenced by some of the cases of Oppenheimer [5] and by the recent report of Baggenstoss and Keith.[7]

REPORT OF CASES

CASE 1.—*History.*—J. B., a 6 week old infant of Italian parentage, was admitted to the Babies Hospital on Aug. 4, 1938. The complaint on admission was "twitchings" of the extremities for four days. The father and mother were alive and well. There was no consanguinity in the parents, and there was no history of familial disease. Pregnancy was not complicated by any known toxemia. One sibling, the result of the only other pregnancy, had died during the first day of life after a difficult breech delivery following seven and one-half months' gestation.

The infant was born with normal delivery three weeks before expected term. He weighed 6 pounds 6 ounces (2,892 Gm.) and was considered normal. Slight jaundice was present during the first four days of life. The infant was nursed for four days with difficulty. He was then given a formula of evaporated milk, water and cane sugar, which was taken poorly. Because of failure to gain weight the patient was given a transfusion of blood at about 12 days of age. At the age of 16 days he was discharged as "well" from the hospital in which he was born. His weight at the time of discharge was 5 pounds 11 ounces (2,580 Gm.). At home he did somewhat better, gaining at about half the expected rate. Orange juice was introduced gradually up to a total of 2 ounces (60 cc.) daily. Percomorph liver oil was given in doses of 3 drops per day (approximately 500 U. S. P. units of vitamin D).

Four days before admission intermittent "twitchings" of the left arm and leg were noted. At first these occurred only when the patient was awake, but later slight abnormal movements were seen when the patient was asleep. On the day prior to admission the right side of the body began to twitch. No loss of consciousness or generalized convulsions were observed. There was no fever, vomiting or complaints referable to the genitourinary tract.

Physical Examination.—At the time of admission, examination revealed an infant of a dusky hue who appeared seriously ill. His weight was 2,890 Gm. and his length 47 cm. There were convulsive twitchings more marked on the left side, usually of one but occasionally of all four extremities, lasting a few seconds each. There was no deviation of the eyes or head or loss of consciousness. The contour of the head and the size and tension of the anterior fontanel were within normal limits. There was no craniotabes. The left ear drum bulged slightly, but the right one appeared normal. The eyes appeared normal. There was a slight nasal discharge, and the pharynx was congested. Respirations were deep and somewhat slow, with periods of irregular breathing, suggestive of Cheyne-Stokes respirations. The lungs were normal on percussion and auscultation. The heart sounds were of good quality with a rapid and regular rhythm. There was a soft systolic murmur localized over the apex. The abdomen was scaphoid. The lower margin of

7. Baggenstoss, A. H., and Keith, H. M.: Calcification of the Arteries of an Infant, J. Pediat. **18**:95, 1941.

the liver was firm and was palpable 2 cm. below the costal margin in the right midclavicular line. The tip of the spleen was felt at the costal margin. The kidneys could not be palpated. The genitals appeared normal except for a mild degree of hypospadias. The urinary stream was normal. The extremities showed no structural abnormalities. Kernig, Trousseau and Chvostek signs were absent, and there was no stiffness of the neck. During some of the more marked periods of twitching there was a suggestion of carpopedal spasm. The deep reflexes were active and equal on the two sides. The skin showed marked loss of turgor. Several attempts to determine the blood pressure were unsuccessful.

Laboratory Examination.—The initial blood count showed 3,570,000 red cells and 35,000 white cells per cubic millimeter, with 52 per cent polymorphonuclear leukocytes, 39 per cent lymphocytes, 2 per cent monocytes and 6 per cent eosinophils. The hemoglobin content was 11 Gm. per hundred cubic centimeters. After the first week the white blood cell count ranged between 7,000 and 12,000, with a differential count which was normal except for an occasional increase of eosinophils up to 9 per cent. The calcium, phosphorus and nonprotein nitrogen determinations are outlined in figure 1. The fasting blood sugar content on admission was 107 mg. per hundred cubic centimeters. The blood urea nitrogen on five occasions between Oct. 12, 1938 and Jan. 4, 1939 varied from 56.7 to 71.7 mg. per hundred cubic centimeters. The ratio of urea nitrogen to the total nonprotein nitrogen in the blood during the same period varied from 78.2 to 97.2. The creatinine content of the blood on August 22 was 2.34 mg. per hundred cubic centimeters. The serum phosphatase concentration on September 12 was 6 Bodansky units, and on November 8, it was 7.3 Bodansky units. The carbon dioxide content of the serum varied between 8.5 and 38.5 milliequivalents per liter on five determinations. The serum chlorides varied between 85.7 and 108.8 milliequivalents per liter on seven determinations. The serum cholesterol amounted to 210 mg. per hundred cubic centimeters, with a ratio of combined to free cholesterol of 1.88. The concentration of serum albumin was 3.84, 3.91 and 4.43 Gm. per hundred cubic centimeters on three occasions. The corresponding figures for serum globulin were 2.9, 2.2 and 2.18 Gm. per hundred cubic centimeters. The specimen of urine obtained on admission was cloudy and acid to litmus. A slight reaction for albumin was given, but no sugar or acetone was found. The test for occult blood with benzidine showed a 2 plus reaction. Microscopic examination revealed many leukocytes and occasional erythrocytes. On numerous examinations the specific gravity ranged between 1.006 and 1.008, rising only twice to 1.014. The Kline precipitation test of the blood serum gave negative results. No organisms were grown from a culture of the blood. Cultures of the urine were positive for Bacillus lactis aerogenes and frequently also for Streptococcus viridans and Staphylococcus albus during the first three months of hospitalization. Spinal fluid obtained by lumbar puncture showed no abnormalities.

Course.—The patient was given an intravenous infusion of 5 per cent dextrose in Ringer's solution and hypodermoclyses of Ringer's solution. A paracentesis of the left ear drum was performed, resulting in a purulent aural discharge. A specimen of urine for culture, obtained by catheterization, showed B. lactis aerogenes.

During the first month in the hospital the patient was afebrile except for having three temperature readings between 100 and 100.8 F. Episodes of hyperpyrexia then developed, associated with bouts of vomiting, which continued throughout his course. The convulsive twitchings gradually diminished in intensity and duration during this period, although they continued to a lesser extent for the remainder

of the infant's life. He took a formula of evaporated milk, water and cane sugar with a value of 110 calories per kilogram of body weight per day. In addition, 10 drops of percomorph liver oil daily, approximately 1,500 U. S. P. units of vitamin D, was administered until the age of 3 months. After this 2 drops of drisdol (vitamin D_2) in propylene glycol was given for six weeks. This was the equivalent of more than 400 U. S. P. units of vitamin D per day. Eight drops of drisdol in propylene glycol, or 1,600 U. S. P. units of vitamin D, was administered daily from the age of 4½ months until death. This is four times the usual dose. Cereal was first given and was taken well at 4½ months of age; vegetables were given a month later. During the entire period the infant vomited one to three times a day about four days a week on the average. Episodes of mild diarrhea occurred, with small amounts of mucus and rarely of blood in the stools. Several cultures of the stools revealed no pathogenic organisms of the group which did not ferment lactose.

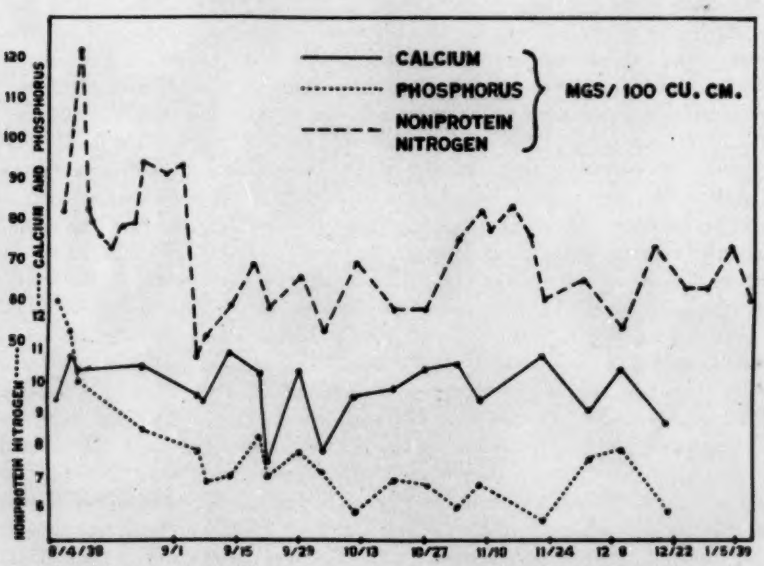

Fig. 1 (case 1).—Variations in the calcium, phosphorus and nonprotein nitrogen contents of the blood.

Therapy was directed at the infection of the urinary tract and at the anemia, and attempts were made to discover the underlying pathologic changes in the genitourinary tract. A roentgenogram of the abdomen taken four days after admission showed nothing significant. The upper parts of the urinary tract were not visualized with two intravenous pyelograms. A cystogram showed the bladder to be slightly dilated. Dye passed retrograde from the bladder to outline an elongated and dilated left ureter and left renal pelvis. Cystoscopy when the child was 3 months old showed no abnormalities of the bladder; both ureteral orifices were visualized. Another cystogram was made at the same time with the patient inverted, in an effort to visualize the upper part of the urinary tract on the right side. The left ureter and renal pelvis presented an appearance similar to that seen on the previous cystogram. On the right side a convoluted ureter of approximately normal caliber was demonstrated. There was definite blunting of the

calices on this side, although the renal pelvis itself was only slightly dilated. These studies indicated bilateral dilatation of the upper parts of the urinary tract, more marked on the left. In the absence of any demonstrable point of obstruction to urinary flow, the diagnosis of neuromuscular vesical dysfunction was therefore made.

As therapy for the infection of the urinary tract sulfanilamide was administered in daily doses of 0.4 Gm. for four days and was continued in half this dosage for three weeks more. At the end of this period a smear of the urinary sediment revealed no organisms or pus cells, but culture of the urine remained positive for B. lactis aerogenes. On one occasion an alpha streptococcus was isolated from the urine. Medication was discontinued temporarily because of the acidosis it produced, but within a week the urine again showed numerous pus cells both singly and in clumps and many gram-negative rods. Sulfanilamide therapy was therefore reinstituted and continued with one brief interruption until three days before death. The concentration of the drug in the blood was generally between 9 and 11 mg. per hundred cubic centimeters and never below 3.5 mg. During the last two months the infection of the urinary tract was largely overcome, since catheterized specimens of urine showed only rare single leukocytes and smears revealed no organisms. The last culture, taken two months before death, was positive for Strep. viridans.

The persistent anemia was treated with repeated transfusions of citrated blood, numbering twenty-four for a total of 1,170 cc. The lowest level to which the hemoglobin was allowed to fall was 7.3 Gm. per hundred cubic centimeters, and the lowest total erythrocyte count was 1,900,000 per cubic millimeter. The interval between transfusions was gradually increased.

The acidosis was difficult to control. Small doses of sodium bicarbonate, up to 0.3 Gm. daily, with larger doses of a sixth-molar solution of sodium lactate resulted in wide fluctuations in the carbon dioxide–combining power of the plasma. Eventually this was maintained at a fairly even level of about 34 volumes per cent by the administration of 3.6 Gm. of sodium bicarbonate by mouth in a 50 per cent solution daily.

A roentgenogram of the distal two thirds of the upper left extremity when the patient was 7 weeks of age showed no abnormal shadows in the soft parts. Three weeks later tubular shadows of calcium density were seen in the region of the large vessels in the left antecubital region, extending about half the length of the arm and forearm in either direction. The first roentgenogram of the lower extremities, made at the same time, revealed calcification of the vessels along the medial aspects of the thighs extending at least as far as the proximal portion of the shafts of the tibias. Roentgenograms of the abdomen and skull showed no similar shadows. Repeated roentgenograms of the extremities during the next two months showed steady increase in the vascular calcification. In the upper extremities the most distal visible calcification was at the level of the distal end of the shaft of the radius (fig. 2). In the lower extremities the shadows terminated at the ankle. Proximally these could be visualized crossing the inguinal region to the pelvis. The first lateral roentgenogram of the neck, taken when the infant was 4½ months old, showed two tubular shadows of calcium density in the region of the thyroid. These were later found to be calcified laryngeal vessels. The larger vessels of the neck were not visualized. The first roentgenogram of the chest, taken at this time, revealed calcified vessels in both axillas. No calcification of the vessels of the hand, skull, thorax or abdomen was demonstrated roentgenographically during life. The cardiac shadow was small. Skeletal maturation was

normal at the carpus at different ages. There was never any definite evidence of rickets. Changes were first remarked in the shafts when the infant was 4½ months old; these consisted of coarsening of the trabecular markings with generalized osteoporosis of the long bones. The same changes were still present when the last set of roentgenograms was taken three weeks later, one month before death. Transverse lines of increased density were present near the ends of the shafts of the long bones.

The patient gained slowly in weight, reaching a maximum of 4,960 Gm. two weeks before death. At 4½ months his total length was 57 cm. and at 5½ months 58 cm. Mild craniotabes of the right parietal bone and slight craniotabes of the left was noted when the patient was 4½ months old. This increased slightly during the following month. No beading at the costochondral junctions and no thickening at the epiphyses was ever found. The cardiac murmur gradually increased from the soft apical systolic blow noted on admission to the hospital to a loud, moderately harsh murmur heard over the entire precordium, loudest

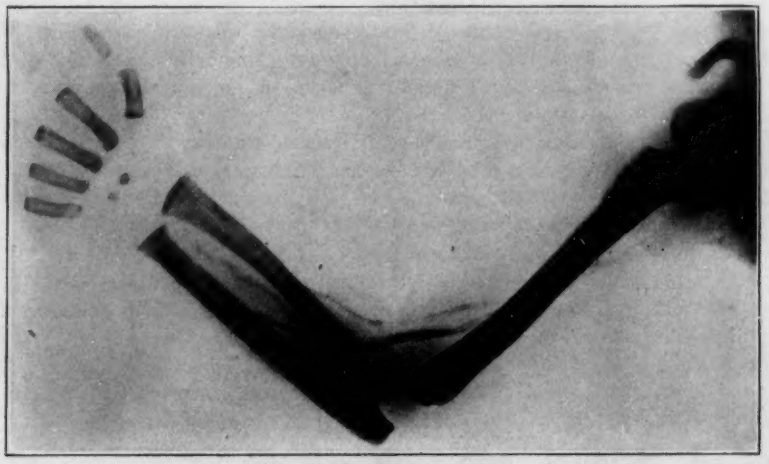

Fig. 2 (case 1).—Calcification of the arteries in a child 4 months old. The radius and ulna show coarse trabeculation.

along the left sternal border. The arteries of the extremities became palpable and hard. Numerous unsuccessful attempts were made to measure the blood pressure both by a sphygmomanometer and with the aid of an oscillometer. No electrocardiogram was taken. The bouts of fever increased in frequency and intensity; two cultures of blood taken at the height of the fever were sterile. Six days before death fever again appeared, the temperature reaching a high level of 106.6 F. Respirations became more rapid and somewhat labored and irregular, and marked irritability developed. The heart sounds became faint, and mild cyanosis appeared. A few minutes before death the patient was noted to yawn frequently, and respirations ceased quietly. Death occurred on Jan. 9, 1939, five months after admission.

Clinical Diagnosis.—The following clinical diagnoses were made: chronic nephritis, congenital malformation of the kidneys, bilateral hydronephrosis and calcification of the arteries of the extremities.

Postmortem Macroscopic Observations.—External examination revealed the body of a moderately well developed and nourished but very pale infant of 6½ months, weighing 4,750 Gm. and measuring 60 cm. in length. Aside from slight craniotabes and moderate prominence of the superficial veins of the upper part of the abdomen, no abnormalities were noted externally or in the body cavities.

The heart weighed 28 Gm. (normal 31 Gm.). All the chambers were moderately dilated. The coronary arteries stood out as hard, irregular, tortuous cords. On section the walls were thick and hard and the lumens narrow. In the right coronary artery there was occlusion, beginning at about the middle of the right ventricle and continuing down the posterior interventricular groove. The posterior wall of the left ventricle and the adjacent portion of the interventricular septum appeared infarcted. The myocardium in this area was mottled and uneven in consistency. The papillary muscle of the anterior leaflet of the tricuspid valve also

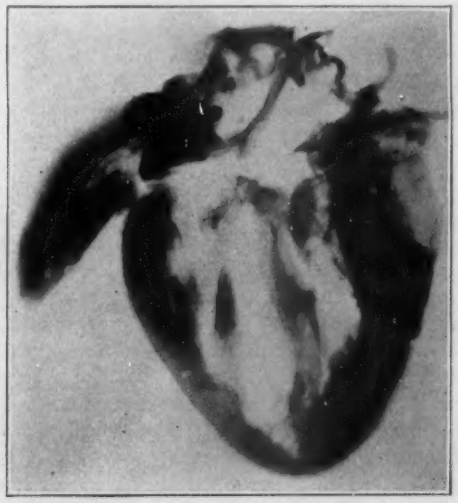

Fig. 3 (case 1).—Roentgenogram of the heart taken at autopsy. The coronary arteries and one papillary muscle were calcified.

contained a gray scar surrounded by mottled myocardium. The valves were normal. The foramen ovale was patent by a narrow slit.

The presence of calcium in the vessels and myocardium was confirmed by a roentgenogram of the heart, taken post mortem (fig. 3).

Kidneys: The right kidney weighed 7 Gm. (normal weight 26 Gm.) and measured 4 by 2 by 2.3 cm. The capsule stripped with much difficulty and showed a pale granular and irregular surface. There were many cysts which varied in size from some which were barely visible to those which measured 2 mm. in diameter. There were scattered petechial hemorrhages, some of which appeared to be within the cysts. The cut surface showed an irregular cortex which could not be readily distinguished from the pyramids and which contained countless minute cysts. The pelvis was bifid and slightly dilated. The small arteries in the hilus were thick and prominent. The ureter was thick walled but not dilated, with a deeply ridged, pale mucosa. A small accessory renal artery arose from the aorta at a point 1.8 cm. below the normal one, passed behind the ureter and entered the medial aspect of the lower pole of the kidney.

The left kidney weighed 10 Gm. (normal weight 25 Gm.) and measured 4.8 by 2.6 by 2 cm. The capsule stripped with difficulty. The surface of the kidney resembled that of the right, except that it was still more irregular. On section the whole wall varied from 1.5 to 6 mm. in thickness and appeared to be composed entirely of fibrous tissue in the thinner portions. In the thicker areas the appearance was similar to that of the right kidney. The pelvis was bifid and markedly dilated and bore a pale and somewhat roughened mucosa. The left ureter was dilated throughout, measuring 6 to 10 mm. in circumference, and was extremely tortuous. No obstruction was found along its course or at the point of entrance to the bladder.

Peripheral Arteries: The innominate artery branched in the usual manner. The right axillary artery appeared normal until the point where the subscapular artery was given off. Distal to this it was irregular in thickness and firm on palpation. The lumen was narrow; the intimal surface was roughened, and hard small granulations could be felt. A crackling sound could be heard on scraping the intima. This continued throughout the portion of the brachial artery which was obtained, namely, that which extended to about the point of the antecubital fossa, and it was also true of the first parts of the small branches which led off from it. The right internal carotid artery appeared normal on external examination and could not be removed. The inferior thyroid artery was small, and on section it appeared thick walled. The superior thyroid artery on the right was tortuous and rigid, and the lumen was small. The arteria thyroidea ima was given off from the innominate artery at a point 7 mm. from the origin of the latter. It was tortuous and hard and contained gritty material. The left carotid and thyroid arteries resembled those on the right. The left subclavian artery appeared normal until it reached a point just beyond the origin of the subcapsular artery. Here it suddenly became narrow. The intima was rough, and the wall was calcified. The circumference dropped from 4 to 2.5 mm. No large arteries were given off in the interim. The entire vessel was quite rigid. The intercostal vessels which were given off from the thoracic aorta were small and thick walled and stood out rigidly from the aortic wall. The branches of the abdominal aorta showed similar changes. The celiac artery appeared normal until its first branch, but the splenic and left and right gastric arteries were all thick walled and contained calcium down to the smallest branches that could be dissected. The superior mesenteric artery was likewise normal near its orifice, but the branches throughout the mesentery were thick and rigid, with pale granular surfaces which crackled and felt hard on scraping. The renal vessels have been described. They were somewhat more elastic than the branches supplying the stomach and intestine. The lumens appeared narrow, however. The intima did not contain obvious deposits of calcium. The wall was thick and firm. The lower artery of the right kidney overlay the inferior vena cava. The inferior mesenteric artery was small and narrowed from its beginning. The common iliac arteries were somewhat rigid, with thick walls but a smooth intima. Both internal and external branches showed thick calcified walls and narrow lumens. Similar changes were found in the right femoral artery and its branches as far as the junction of the middle and lower thirds of the thigh. The left internal iliac and femoral arteries were similar. The vessels of the circle of Willis and the basilar artery appeared normal. The right vertebral artery, proximal to its junction with the basilar artery, was firm and calcified.

Parathyroids: The parathyroids occupied their normal positions and appeared large and pink. They were dissected out and weighed. The right upper gland weighed 11.9 mg.; the right lower, 16.1 mg.; the left upper, 11.8 mg., and the

left lower, 19.5 mg., with a total of 59.3 mg. For comparison, the parathyroids have been weighed in subsequent autopsies. The average weight of eighteen glands from 6 infants between the ages of 5 and 7 months without renal pathologic changes was 2.9 mg., with a range of 0.9 to 4.8 mg. In 3 of these infants four or more glands were found, and in these 3 the total weight of the parathyroids was 7.3, 12.4 and 14.3 mg. respectively.

Bones: No gross abnormalities were noted.

Other Organs: The lungs gave evidence of recent lobular pneumonia. The spleen, liver, pancreas, adrenals, pelvic organs, alimentary tract, brain and organs of the neck showed no significant abnormalities.

Bacteriologic Examination.—A culture of postmortem blood showed Bacillus acidi lactici and Staphylococcus albus haemolyticus. Culture of material from the lungs showed Strep. viridans and B. acidi lactici.

Postmortem Microscopic Examination.—Heart: Eight sections were taken from various portions of the heart. In those taken from the anterior portions of the right and left ventricles the myocardium was normal. The septum and the posterior wall of the left ventricle showed extensive fibrosis, with scattered small groups of necrotic muscle fibers and rather large deposits of calcium in the fibrous areas. Masson's trichrome stain emphasized the abundance of fibrous tissue. One papillary muscle showed similar fibrosis and calcification. The myocardium of the left auricle was somewhat fibrosed, and a large plaque of calcium lay beneath the endocardium. The two main branches of the left coronary artery showed extensive medial calcification (fig. 4). In one of them there were a few muscle fibers external to the mass of calcium and some fibrous proliferation of the media; an elastic tissue stain showed a single heavily stained inner elastic membrane, with a coarse network of elastic fibers in the adjacent intima. In the other, the entire media was replaced with calcium, and the lumen was almost entirely obliterated by the thick intima, which was composed of loose fibrous tissue containing many fibrocytes. There was some evidence of canalization. The stain for elastic tissue showed only a few fragments of the inner elastic membrane. There were scattered elastic fibers in the intima. The right coronary artery also showed calcification of the media and proliferation of the intima. In addition, there were irregular deposits of calcium in the deeper portion of the intima. The calcium was identified by the use of the von Kossa stain.

Aorta: Sections from the ascending portion of the aorta gave the impression of some muscular hypertrophy but showed no other abnormalities. The abdominal aorta was normal.

Peripheral Arteries: In the brachial artery the media was replaced by large irregular deposits of calcium separated by small amounts of fibrous tissue. The intima was thickened by hyperplastic connective tissue so that only a small lumen remained. Some of the plaques of calcium in the media extended into the intima.

One of the right internal and external iliac arteries resembled the brachial artery except that for about one eighth of the circumference the wall was free from calcium; the other vessel contained large masses of calcium, so that the structure was somewhat obscured and the lumen was obliterated. An elastic tissue stain showed normal elastic membrane in the small noncalcified area; elsewhere only short irregular fragments of elastic tissue were found. A von Kossa stain confirmed the presence of large plaques of calcium in the media and in the inner elastic membrane.

The right femoral artery was essentially similar to the preceding.

In the splenic artery the entire media was replaced by calcium for about one fourth of the circumference but appeared normal elsewhere. The intima over

this plaque showed slight proliferation. The inner elastic membrane was thick and calcified along most of the circumference. At one point the inner elastic membrane appeared broken, and there was an irregular intimal plaque of calcium. A von Kossa stain showed much calcification of the inner elastic membrane and a large plaque of calcium in the media.

Right Kidney: At one end of the section the wall was fairly thick and was composed of large numbers of cystlike spaces lined with cuboidal epithelium. Some of these opened into one another as though they were formed from dilated tubules. A few glomeruli were present and appeared hypertrophied with an

Fig. 4 (case 1).—Coronary artery with intimal proliferation and calcium in the media (torn).

increase of nuclei. The interstitial tissue was increased in amount and composed of fibrous tissue and scattered lymphocytes and phagocytes, some of which contained brown pigment. In another portion of the wall the cortex measured only 0.2 mm. in thickness. It consisted almost entirely of fibrous tissue in which there were scattered atrophic glomeruli, many of which were fibrosed. There was an increase of fibrous tissue in the pyramids also, and some of the remaining tubules were filled by casts. The pelvic epithelium appeared normal. A phosphotungstic acid stain showed thickening of the basement membrane around the tubules and also in the glomeruli. The von Kossa stain showed no calcium.

Left Kidney: The entire wall was about 0.8 mm. in thickness. The microscopic structure was similar to that of the right kidney, with the addition that the pelvic mucosa was fibrosed and infiltrated with lymphocytes.

Parathyroids: The cell outlines were regular in size and enclosed a pale cytoplasm which in some cases contained a few faintly basophilic granules. The nuclei varied somewhat in size and depth of stain.

Rib: The epiphysial line showed slight irregularity. The columns of proliferating cartilage cells were unusually long and varied in length in different areas. A group of vessels entered the cartilage between the resting cartilage and

Fig. 5 (case 1).—Epiphysis, showing irregular trabeculae and an increase in osteoclasts.

the proliferating zone. At the epiphysial line the uncalcified cartilage matrix extended in long and irregular columns into the shaft marrow, and islands of this material were scattered through the marrow for a distance of 0.8 mm. In the first 2 mm. from the epiphysial line the trabeculae were quite irregular (fig. 5). The marrow spaces contained fibrous tissue in which there was much hemorrhage, and there were large numbers of giant cells having many nuclei, often ten to fifteen. In this region the trabeculae were often composed of a central zone of uncalcified cartilage matrix surrounded by an irregular calcified area, the whole surrounded by a very narrow zone of osteoid against which there was a line of osteoblasts, with these giant cells among them. At a slightly greater distance from the cartilage the trabeculae became greatly thickened (figs. 6 and 7).

Fig. 6 (case 1).—Rib shaft, showing a thick cortex, wide trabeculae and osteitis fibrosa.

Fig. 7.—Rib shaft from a case of rickets for comparison with figure 6. The trabeculae are thin; there is subperiosteal bone formation, and the marrow is normal.

The osteoid zone was narrow or absent. Osteoclasts were less numerous, and the marrow spaces were filled with a loose fibrous tissue. There was also some irregularity in the shaft near the epiphysis. Beginning at a point approximately 1 cm. from the epiphysis the marrow spaces contained some hemopoietic tissue. The spaces nearer the cortex were still largely occupied by fibrous tissue, and occasional groups of giant cells were found here. In this portion of the shaft the trabeculae were wide and quite irregular in thickness and in pattern. The marrow appeared normal except for the presence of large masses of greenish brown pigment within the phagocytes. Similar pigment was deposited beneath the periosteum. The brown pigment took the stain for iron.

Humerus: The appearance was closely similar to that of the rib. Hemopoietic tissue was first encountered approximately 1.5 cm. from the epiphysial line.

Vertebrae: The vertebrae appeared to be similar to the rib and humerus.

Other Organs: The changes in the remaining organs are indicated in the anatomic diagnosis.

Anatomic Diagnoses.—The following diagnoses were made: congenital hypoplastic kidneys; hydronephrosis, bilateral; fibrosis of the kidney (from healed pyelonephritis?); hypertrophy of the bladder and ureters (mild); renal rickets (early); medial calcification of the arteries (coronary, bronchial, laryngeal, splenic, gastric, superior mesenteric, brachial, iliac, hypogastric and femoral); infarct of the heart; fibrosis of the myocardium; dilatation of the left ventricle; calcification of the myocardium; hypertrophy of the parathyroids; lobular pneumonia (Strep. viridans and B. acidi lactici); aspiration of vomitus; acute erosion of the esophagus; hemosiderosis of the spleen and liver, and patent foramen ovale.

Case 2.—*History.*—S. S. was admitted to the hospital on June 18, 1939, at the age of 4 weeks, because of convulsions of one day's duration. The family history was irrelevant. Birth was normal, and the birth weight was 6 pounds 14 ounces (3,120 Gm.). The baby appeared normal during the neonatal period. About two weeks before admission he began to have abdominal cramps, during which his abdomen became hard and he would draw up his legs. Occasional starting movements and jerkiness were noted. On the night before admission he had the first of a series of convulsions. These were bilateral and recurred at about ten minute intervals until admission.

Physical Examination.—On admission the infant appeared well nourished but twitched frequently and went into a convulsion while being examined. His weight was 3,880 Gm. and his length 53 cm. The anterior fontanel was open. There was no craniotabes, although there was softening along the right parietal suture. The epiphyses were not enlarged, and there was no bony tenderness. The skin showed a diffuse papular rash. Palpation of the abdomen revealed a large firm rounded mass in the right flank. The reflexes were hyperactive, and there were Chvostek and Trousseau signs and peroneal reflexes suggestive of tetany.

Laboratory Examination.—On admission the hemoglobin content was 12 Gm. per hundred cubic centimeters (88 per cent). The red blood cell count was 3,410,000 and the white blood cell count 34,800 per cubic millimeter, with 83 per cent polymorphonuclear cells. Subsequent examination showed a variable degree of anemia, the lowest hemoglobin value being 6.6 Gm. per hundred cubic centimeters (46 per cent). On admission the calcium content of the serum was 9 mg. and the phosphorus content 11.3 mg. per hundred cubic centimeters. Numerous later examinations revealed wide variations in both calcium and phosphorus content, but at no time was the calcium-phosphorus product below 50. At first the calcium content was within the normal range, but during the last six weeks of life it

was always low, usually between 6.5 and 7.4 mg. per hundred cubic centimeters. Throughout the course the phosphorus content usually lay between 8 and 10 mg. per hundred cubic centimeters, the maximal range being 6.4 to 11.3 mg. The amount of nonprotein nitrogen varied between 68.4 and 125 mg. per hundred cubic centimeters. The carbon dioxide-combining power was always low, usually between 16 and 28 volumes per cent, the highest being 41.4. On one occasion the value for phosphatase was 11.36 Bodansky units. On August 14 the total serum cholesterol amounted to 177 mg. per hundred cubic centimeters, with a ratio of combined to free cholesterol of 3.27. The serum albumin was 4.38 Gm. and the serum globulin 3.06 Gm. per hundred cubic centimeters. On October 2 the urea nitrogen content was 96.1 mg. per hundred cubic centimeters. The ratio of the urea nitrogen to the total nonprotein nitrogen of the blood was 94. The reactions to Kline and tuberculin tests were negative.

Examination of the urine on admission showed a specific gravity of 1.002; the reaction was alkaline, and there was a heavy trace of albumin. Tests for sugar and acetone gave negative results, as did the microscopic examination. Later tests gave similar results. The highest specific gravity was 1.012. Cultures of catheterized urine showed a few colonies of Staph. albus and Staphylococcus aureus.

Roentgenograms, taken at 1 month of age and again at 2½ months, showed no abnormalities in the wrist and knee. When the infant was 4 months old the wrist showed no evidences of rickets at the cartilage-shaft junctions; however, there were a coarsening of the shaft markings similar to that seen in case 1 and some demineralization of the skeleton. At no time was there evidence of calcification of the peripheral arteries. There were shadows of calcium density in the gluteal regions. Cystograms showed no retrograde flow into the ureters. Attemps to obtain a retrograde pyelogram and also an intravenous pyelogram were unsuccessful. Flat plates of the abdomen showed no abnormalities. An electrocardiogram showed sinus tachycardia.

Course.—The child was given 1 Gm. of calcium gluconate intramuscularly and 1 Gm. of calcium chloride by mouth, and on the day after admission he received 300,000 U. S. P. units of vitamin D in the form of vitamin D_3 (irradiated 7-dehydrocholesterol). Convulsions were controlled by the day after admission. The administration of calcium chloride was continued for two more days, the total dose at this time being 3 Gm. The baby was kept on a formula of evaporated milk and cane sugar with ascorbic acid. His blood pressure on the third day was 122 systolic and 64 diastolic. The fundi were normal. He received no further vitamin D therapy until he was 3½ months old. At this time he received 6 to 8 drops of viosterol in oil daily for one week, after which the dose was increased to 15 drops. This dose was continued until his death. At 4½ months he was given 5 cc. of 10 per cent calcium gluconate intramuscularly, daily, for three days. During the last three weeks of life he received 4 Gm. daily of calcium gluconate by mouth. Small transfusions were given from time to time to combat the chronic anemia. Sodium lactate was given by mouth on several occasions in an attempt to raise the carbon dioxide-combining power. Three weeks before death a large area of aseptic necrosis appeared on the left buttock at the site of the injections of calcium gluconate. Shortly before death the nonprotein nitrogen content rose to 125 mg. per hundred cubic centimeters and the carbon dioxide-combining power fell to 16 volumes per cent. During the latter part of the course the blood pressure ranged between 136 systolic and 90 diastolic and 150 systolic and 90 diastolic. Death was sudden.

Clinical Diagnosis.—The following diagnoses were made: congenital polycystic kidneys, chronic uremia and tetany, due to a low calcium content of the serum.

Postmortem Macroscopic Examination.—The body was that of a well developed and well nourished white boy aged 6 months, weighing 5,880 Gm. and measuring 62.5 cm. External examination showed few abnormalities: The abdomen was distended, and both buttocks bore indurated red areas, with a small dry central ulcer on the left. The examination was restricted to an abdominal incision. In the abdominal cavity a cystlike structure measuring 4.4 by 5 by 4.5 cm. was found in the midline above the bladder. This was found to be the greatly dilated pelvis of the right kidney. A ureter of normal diameter arose at the lower pole of the cyst and passed to the normal bladder. The cecum and proximal third of the ascending colon were mobile.

Heart: The heart weighed 43 Gm. (normal weight 29 Gm.). It appeared normal except for dilatation and hypertrophy of the left ventricle. The coronary arteries showed no abnormalities.

Aorta: The intima bore a thickened plaque about 4 mm. wide extending from the orifices of the first intercostal arteries to the bifurcation of the aorta.

Kidneys: The left kidney weighed 18 Gm. after fixation (normal weight 25 Gm.) and measured 4.4 by 3.7 by 2.4 cm. It was a somewhat flattened spheroid, lobulated mass, made up of numerous closely approximated pale gray tense cysts. These varied in diameter from 0.2 to 2.2 cm. A moderate amount of perirenal fat could be stripped away. On section the organ was composed of numerous cavities lined by smooth pale gray tissue. The walls of the cysts were paper thin, and the cavities contained clear fluid. Between the cysts lay loose connective tissue and blood vessels. No renal parenchyma was visible. The renal pelvis was not found.

The left ureter was narrow. It measured 4 mm. in its widest portion but narrowed to a diameter of 1.5 mm. at a level 1 cm. below its attachment to the kidney. A lumen could not be demonstrated in the proximal 2 cm. of the ureter, and it appeared here to be a fibrous cord which broadened out into a band at its insertion to the kidney. A branch from the renal artery entered the kidney slightly above the site of attachment of the ureter. The artery measured 2 mm. in diameter.

The right kidney and pelvis weighed 56 Gm. after fixation (normal weight 25 Gm.) and measured 6.7 by 6.3 by 4.2 cm. The capsule stripped with difficulty, revealing a pale pinkish white, lobular, firm kidney. The surface was extremely pale but flecked with small reddish areas, many of which appeared to be congested blood vessels. Fetal lobulation was prominent. The pelvis was dilated, forming the large cyst previously described. The cut surface of the kidney was extremely pale, and the cortex and pyramids could not be made out, though pink striations could be seen in a few areas. There were two large intrarenal pelves, each about 2 cm. in diameter, lined with smooth grayish white mucosa. Each pelvis was continuous with the dilated extrarenal pelvis, to the tip of which the ureter was attached. There was no exudate on the mucosa of the pelvis. The proximal end of the right ureter crossed over and was fixed to the dilated pelvis in such a manner that there was an angulation at the ureteropelvic junction. As seen from the internal surface of the dilated pelvis, there was a narrow slitlike orifice, 5 mm. in length, into which a fine probe could be passed, but it did not pass the site of the ureteral angulation. After the ureter was dissected free from the renal pelvis, however, its proximal 1.5 mm. was found to measure 2 mm. in diameter, and a small orifice, admitting a probe less than 1 mm. in diameter, was demonstrated at the ureteropelvic junction. Below the site of constriction the ureter was of normal caliber. Two branches from the right renal artery entered the hilus of

the kidney above the dilated pelvis. After fixation the anterior and posterior arterial branches each measured 2 mm. in diameter.

Parathyroids: Because of the limitations of the incision the organs in the neck were incompletely removed. One parathyroid, believed to be the lower one on the left side, was obtained, and this weighed 27.2 mg. (control figures given in case 1: 0.9 to 4.8 mg.).

Rib: The costochondral junction showed slight beading. On section the epiphysial line was narrow and regular. Beneath it was a pale gray zone of bony consistence about 5 mm. wide. The marrow was slightly pale, mottled red and pale gray. The cortex felt firm, and its margins were not sharply demarcated from cancellous bone.

Other Organs: The lungs were edematous. No significant abnormalities were found in the peripheral arteries, spleen, liver, pancreas, adrenals, bladder or gastrointestinal tract. Permission for the removal of the brain was not obtained.

Microscopic Examination.—Heart: Most of the muscle fibers appeared normal, but there were scattered round foci in which the fibers appeared pale, empty and degenerating. Here and there were small round blue masses of calcium, about ⅙ high power field in diameter, surrounded by necrotic muscle fibers, which appeared to represent a later stage of the same process. There was no cellular reaction around these foci, although elongated pale nuclei apparently from muscle cells were present. There was a slight increase in fibrous tissue around some of the arterioles. Sections taken through various parts of the heart were similar.

Aorta: A section taken through the arch showed slight intimal proliferation with reduplication of the inner elastic membrane. Section through the thick plaque in the thoracic aorta showed the intima and media to be of equal thickness at this point. The intimal plaque showed proliferation of the elastic fibers and of the connective tissue, but no fat vacuoles were found. The innominate artery and the left carotid were similar to the aorta.

Coronary Arteries: In the anterior descending branch of the left coronary artery there was a slight proliferation of the intima. The inner elastic membrane was thickened, and much of it was calcified. Instead of the regular undulations which it usually showed in section the membrane showed coarse irregular waves with a break in the calcium at each bend, giving the impression that the calcium acted as a splint (fig. 8). There was no cellular reaction. The media and adventitia appeared normal. In the circumflex branch of the left coronary artery the intima was thickened so as to reduce the diameter of the lumen by one third. A stain for elastic tissue showed fragmentation of the inner elastic membrane and proliferation of the elastic fibers throughout the thickened intima. The media and adventitia were normal.

The celiac axis, right renal artery, small mesenteric arteries, femoral and hypogastric arteries were similar to the anterior descending branch of the left coronary artery, with calcification of the inner elastic membrane and intimal proliferation. The left renal and superior mesenteric arteries were similar except for the absence of calcium. The pulmonary artery appeared normal.

Left Kidney: The section showed a series of cysts varying in diameter up to 3.6 mm. The smaller ones were lined by cuboidal epithelium and the larger by flat cells. The lumens were empty or contained small amounts of protein precipitate. Between the cysts there was a small amount of connective tissue infiltrated with a few lymphocytes and containing occasional small glomeruli. The glomeruli were atrophic, fibrosed or sometimes calcified; none appeared normal.

Right Kidney: The glomeruli were much decreased in number; many were fibrotic, and some were calcified, although a fair number of relatively normal ones

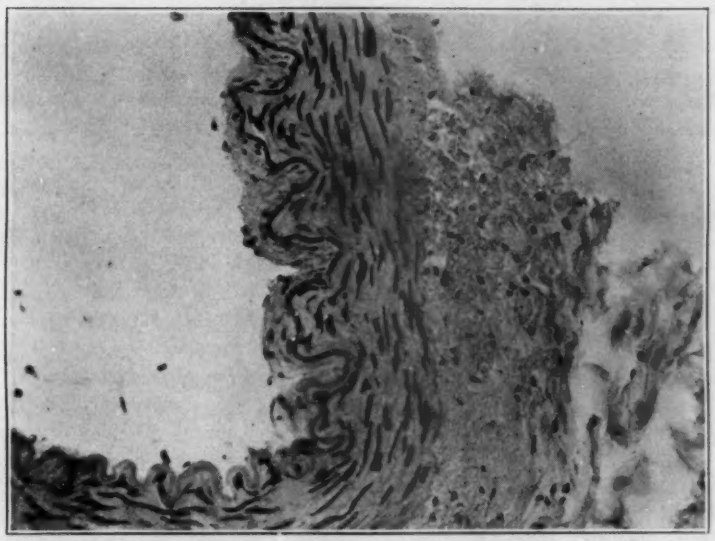

Fig. 8 (case 2).—Right renal artery, with calcification of the inner elastic membrane.

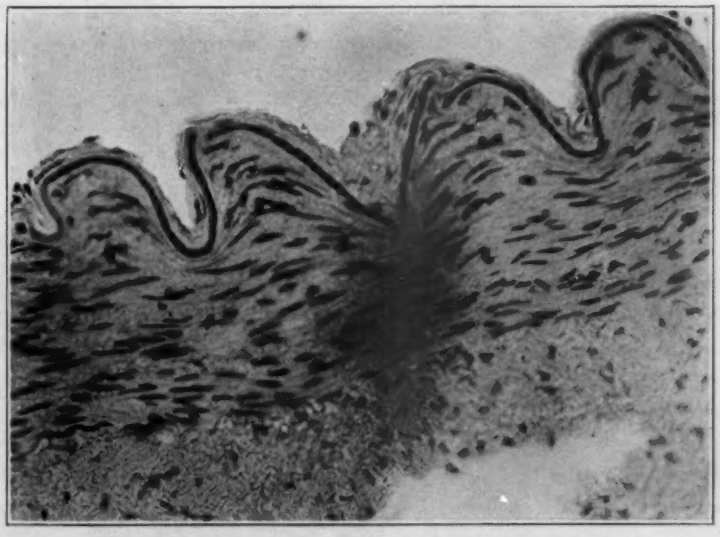

Fig. 9 (case 2).—Femoral artery.

remained. The tubules were much dilated but were lined with normal epithelium; a few contained casts. The connective tissue was greatly increased in amount both in the cortex and in the pyramids, and it was diffusely infiltrated with lymphocytes and a few mononuclear and polymorphonuclear cells and eosinophils. There were many dense accumulations of lymphocytes, especially in the outer portion of the cortex, which involved areas up to 0.8 mm. in size. The presence of calcium in these areas and in some glomeruli was confirmed by the von Kossa stain.

Parathyroids: The gland that was removed was surrounded by a connective tissue capsule, which also included a small portion of thymus tissue, 1 high power field in diameter. The gland was 1.6 mm. in diameter. It was composed of anastomosing cords of large pale cells, among which were a few smaller cells with darker granular cytoplasm. Between the cords the connective tissue was abundant and occurred in wide cellular bands. The blood vessels were normal.

Rib: The epiphysial line was straight, and the zone of preparatory cartilage was of normal width. The trabeculae near the epiphysis were highly irregular in pattern, and most of them contained central masses of calcified cartilage matrix. Along their margins lay densely packed walls of osteoblasts. Between the trabeculae there was loose connective tissue containing large numbers of osteoclasts, some of which were arranged in clusters. This structure changed gradually with the distance from the epiphysis, with coarsening of the trabeculae and a decrease in the number of osteoclasts. The trabeculae were still abnormally thick and irregular with typical lacunas; the osteoblasts remained exceedingly numerous, and the marrow was fibrous. At a point about 6 mm. from the epiphysis the first hemopoietic marrow was seen, and beyond this point there were only scattered areas of fibrosis. The cortex was unusually thick.

Other Organs: The lungs were moderately edematous. The thymus appeared normal except for a deposit of calcium in the connective tissue; no calcium was found in the Hassall corpuscles. Small deposits of calcium were found in the striate muscle. The liver contained small amounts of hemosiderin in the parenchymal and Kupffer cells and also a few fat vacuoles in the former. No significant abnormalities were found in the spleen, pancreas, adrenals, bladder, thyroid and gastrointestinal tract.

Anatomic Diagnoses.—The following diagnoses were made: renal hyperparathyroidism; congenital polycystic kidney (left); atresia of the left ureter; congenital stricture of the right ureteropelvic junction; hydronephrosis (right); hypertrophy of the parathyroids; osteitis fibrosa; calcification of the myocardium, kidneys, arteries and thymus; intimal proliferation of the aorta and arteries; cardiac hypertrophy; edema of the lungs; mobile cecum; hemosiderosis of the liver, and ulcer of the left gluteal region.

COMMENT

The clinical picture is closely similar in the 2 cases. Tetany was the presenting symptom on admission at the ages of 6 and 4 weeks respectively. This was associated with elevated serum phosphorus and nonprotein nitrogen contents of the serum and with acidosis. On admission the serum calcium was low in 1 case and normal in the other, but as time progressed it was increasingly difficult to maintain a normal level in both cases. The renal insufficiency was not at first apparent and was manifested chiefly by the consistently low specific gravity of the urine in

association with a high level of serum nonprotein nitrogen and chronic acidosis. The clinical problem at first seemed one of combating a persistent hypocalcemia and tetany. The appearance of calcified arteries in the roentgenograms in case 1 stimulated further investigation of the urinary tract and discovery of congenital anomalies. The osseous lesions were never conspicuous and were evidenced by coarsening of the trabeculae in the shafts of the long bones.

The essential postmortem observations in both cases were: (1) a severe renal anomaly; (2) hypertrophy of the parathyroids; (3) metastatic calcification involving the middle-sized arteries throughout the body, more marked in case 1, in which the intake of calcium and vitamin D had been greater, and (4) osseous lesions similar to those found in osteitis fibrosa but relatively mild in degree.

COMPARISON OF MANIFESTATIONS OF RENAL HYPERPARATHYROIDISM IN INFANCY, ADOLESCENCE AND ADULT LIFE

These 2 cases do not appear to throw new light on the complex interrelations of the changes in the kidneys, bones, parathyroids and calcium and phosphorus metabolism in renal hyperparathyroidism. They do present some variations from the disease picture as found in later childhood, adolescence and adult life which merit discussion.

1. *Renal Lesions.*—Although the parathyroids are hypertrophied in most types of moderately severe disease of the kidneys, the complete syndrome of hyperparathyroidism appears only in cases in which severe renal damage has been present and has remained fairly stationary for a long time, often for years. In infancy and childhood the disease usually results from a congenital malformation. The types of malformation vary widely, the most common being bilateral hydronephrosis and polycystic kidneys. Glomerular nephritis in childhood rarely if ever produces renal hyperparathyroidism. In later life the lesion may be either a congenital anomaly or an extreme fibrosis resulting from pyelonephritis, glomerulonephritis or vascular disease. The characteristics of the renal lesion at all ages are the severity and the static nature of the pathologic change. The early symptoms are usually polydipsia and polyuria without albuminuria but with a urine of low and often of fixed specific gravity. The terminal symptoms may be those of uremia. Administration of parathyroid extract has been shown to produce polyuria, and it is possible that the polyuria of these patients may be in part due to this factor.

2. *Sensitivity to Variations in Calcium and Vitamin D Intake.*—During the growth period the osseous lesions present a varied and complex picture which is not identical with that found in adult hyperparathyroidism. In addition to osteitis fibrosa, there are sometimes

changes at the epiphyses which are strongly suggestive of rickets due to vitamin D deficiency. In many cases the epiphysial changes are mild or absent, but in other cases they predominate. There is a considerable amount of evidence that patients with renal hyperparathyroidism show an abnormal sensitivity to variations in the calcium and vitamin D intake. Since vitamin D has been shown to increase the absorption of calcium from the intestine, it may be sufficient to say that these patients are unusually responsive to changes in the amount of calcium absorbed. The lesions of true rickets appear on slight provocation; a moderate excess of calcium absorption will produce not only healing of the rickets but also hypercalcification of the bones and deposits of calcium in other tissues, including the arterial media. Even the more fantastic alterations in the bony structure become comprehensible when viewed as the result of intermittent periods of deficiency of vitamin D or calcium superimposed on the lesions of osteitis fibrosa. Evidence for these statements may be found in many of the reported cases, including those presented here. Some of the observations leading to this concept will be summarized here.

The chief evidence for abnormal sensitivity to a low calcium intake is the occurrence of epiphysial lesions characteristic of rickets in late childhood and early adolescence, at an age when rickets is unusual. These changes do not occur in adult renal hyperparathyroidism. That the lesions are due to rickets is proved by their characteristic appearance in roentgenograms and by their response to specific therapy. Parsons [8] studied the osseous lesions of renal rickets roentgenographically and classified them into three types: (1) the atrophic type, with marked osteoporosis and with the epiphysial lesions of rickets; (2) the florid type, with extensive epiphysial lesions, and (3) the woolly type, with coarse and irregular trabeculation but without the epiphysial lesions of rickets. He stated that the epiphysial lesions of the first two types were improved by ultraviolet therapy but that lesions of the third type were unimproved or were made more severe by this means. In cases in which the woolly type of lesion is seen in the long bones the skull shows the changes characteristic of Paget's disease. These changes in the skull are now known to be a characteristic part of the picture of hyperparathyroidism. The first two types appear to represent a mixture of lesions due to renal hyperparathyroidism and to true rickets. The difference between these types is not clear. The third type is now known to be characteristic of pure hyperparathyroidism.

Increased sensitivity to a mild excess of calcium or vitamin D may be found in many of the cases of renal rickets in which there is metastatic

8. Parsons, L. G.: The Bone Changes Occurring in Renal and Coelic Infantilism and Their Relationship to Rickets: I. Renal Rickets, Arch. Dis. Childhood **2**:1, 1927.

calcification. A few of them will be cited to clarify the point. Karelitz and Kolomyzeff [9] reported the following case:

A child 6 years old had her first symptom at the age of 18 months, which was difficulty in walking. This was treated successfully with cod liver oil. At 2 years the child was underdeveloped and pale, and polydipsia and enuresis were noted. In spite of the continued use of cod liver oil the child showed rachitic changes at the epiphyses at the age of 6 years. A genu valgum deformity and Paget's disease of the skull had appeared, and the woolly type of lesion in the long bones was seen in roentgenograms. She was then given viosterol in oil, with healing of the epiphysial lesions but with a gradual increase in the woolly type of osseous lesion. Under this therapy there appeared calcification of the peripheral vessels and other evidences of metastatic calcification. The authors pointed out the occurrence of rickets in the presence of a calcium-phosphorus product of more than 40. The patient died at the age of 8 years. Postmortem examination was not made.

A second case was that of Lightwood.[10]

A child, who was first brought to the physician because she had never grown properly, at 15 months measured 70 cm. in length and weighed 13 pounds (5,900 Gm.). She had never walked. After an attack of diarrhea at 8 months of age she was given a diet composed of equal parts of milk and solution of calcium hydroxide U. S. P. for six weeks. After this she received a normal diet and 1 teaspoonful of solution of calcium hydroxide U. S. P. with each feeding until the age of 1 year. From the fifteenth to the eighteenth month she received cod liver oil daily. On admission at 27 months of age she was a poorly nourished dwarf with biscuit-colored skin, knock knees and carious teeth. There was no beading of the ribs. The peripheral vessels were palpable and were found by roentgenogram to be calcified. The calcium content of the serum was 11 mg. per hundred cubic centimeters and the phosphorus content 6.7 mg. The urea content of the blood was 169 mg. per hundred cubic centimeters, with a poor urea concentration reaction. She died a few days after admission. At autopsy the kidneys were found to be tough, pale, fibrosed and partly calcified. The bones showed no deformity, but there was irregular dense calcification with alternating zones of osteoporosis and osteosclerosis. The epiphysial lines were somewhat wide, and the cartilage was slightly irregular. Next to the epiphysis was a zone of osteoid, beyond which the trabeculae were normal. The skull was very thick. The medium-sized and small arteries throughout the body showed medial calcification. Deposits of calcium were found in many sites, including the tentorium, lung, pleura and stomach. One parathyroid measured 2 to 3 mm. in length (normal), and no parathyroid tumor was found.

The author considered the coincidence of renal lesions with the osseous lesions and metastatic calcification as accidental. We believe this case to be an instance of renal hyperparathyroidism.

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9. Karelitz, S., and Kolomoyzeff, H.: Renal Dwarfism and Rickets, Am. J. Dis. Child. **44**:542 (Sept.) 1932.

10. Lightwood, R. A.: Case of Dwarfism and Calcinosis, Associated with Widespread Arterial Degeneration, Arch. Dis. Childhood **7**:193, 1932.

Our third case, not reported in detail, appears similar to Lightwood's case. The supply of calcium in the body was reenforced by increased absorption due to a large amount of ultraviolet radiation. The renal and osseous lesions were similar. There was microscopic evidence of parathyroid enlargement.

The sensitivity to alterations in calcium and vitamin D intake in these patients raises a difficult therapeutic problem. A deficiency in these substances will produce florid rickets, and a dose within the normal range will produce metastatic calcification, calcification of the arterial media and sometimes infarcts and gangrene.[6] Until experience as to dosage has been accumulated no specific conclusions can be drawn.

3. *The Mild Degree of Parathyroid Hypertrophy and of Osseous Lesions in Infants.*—In our first 2 cases the osseous lesions, although detected roentgenographically, were not conspicuous, and in the 4 comparable cases of calcification of the arteries in infants obtained from the literature no mention was made of pathologic changes in the bones. In our cases the characteristic picture of osteitis fibrosa was found on microscopic study. Oppenheimer [5] considered the parathyroids normal in her cases. In our 2 cases the enlargement was not conspicuous at autopsy, but the weight of the glands was four to eight times the normal. This degree of hypertrophy is mild in comparison with the figures given in adult renal hyperparathyroidism of twenty to one hundred times the normal figure. The moderate degree of these changes in the bones and parathyroids may be interpreted as the consequence of the short duration of the disease. They may, however, be due to the larger amounts of calcium and vitamin D in the diet of the infant as compared with that of the adult. The uniform presence of metastatic calcification in these cases can best be explained on the latter hypothesis. If the sole stimulus capable of producing parathyroid hyperplasia is a low blood calcium level, this view fits the known facts. The two hypotheses—short duration of the disease and relatively high intake of both calcium and vitamin D—do not exclude one another and may both prove to be valid.

4. *Dwarfism.*—It is not surprising that when a disease severely affecting both the bony structure and the renal excretion occurs during the growth period it produces poor development, sometimes to the degree of dwarfism. It is obvious that retardation in growth must be confined to the age when growth is taking place and consequently is absent in cases in which the onset of symptoms was after adolescence. It is less easy to find an explanation for the fairly normal growth in our 2 cases; possibly the absence of the epiphysial changes of rickets may account for it. This raises the question as to how much of the failure of growth in the renal rickets of childhood is due to the epiphysial changes of the type which respond to antirachitic therapy and how much is due to the

osteitis fibrosa lesions of hyperparathyroidism, a question which cannot be answered here. There was marked retardation in 2 somewhat older infants, one aged 27 months (Lightwood [10]) and one aged 14 months, (report of whose case was discovered in our autopsy files).

SUMMARY AND CONCLUSIONS

Two cases of renal hyperparathyroidism in infancy have been described. The presenting clinical picture was that of tetany and acidosis, both resistant to therapy, associated with alterations in the calcium and phosphorus contents of the serum. In the first case intensive antirachitic therapy was given, which was followed by calcification of the small arteries throughout the body and death at the age of 6 months as the result of an infarct of the heart. The second infant, treated more conservatively, showed metastatic calcification of less severe degree. The renal insufficiency was at first inconspicuous and was characterized by urine of low specific gravity, chronic acidosis and an elevated nonprotein nitrogen content of the serum. The essential postmortem observations were a severe renal anomaly, hypertrophy of the parathyroids, osteitis fibrosa and metastatic calcification with medial calcification of the small arteries throughout the body.

The clinical and pathologic manifestations of renal hyperparathyroidism in infancy, childhood and adult life have been compared, with the following chief differences: 1. In infancy and childhood the renal lesion is congenital, but in the adult the renal insufficiency may also result from pyelonephritis, glomerulonephritis or vascular disease. At all ages the renal insufficiency is severe and fairly static. 2. During the growth period there is greater sensitivity to variations in the calcium and vitamin D intake. Severe rickets may occur in late childhood under circumstances which do not usually produce rickets. At any age period a moderate excess of vitamin D, at levels usually harmless, may produce hypercalcification of bones and deposition of calcium in tissues, including the media of the small arteries.

In cases of renal parathyroidism in infancy which we have described, the changes in the bones and parathyroids were less marked than in the reported cases of older children and adults. This may be due to the high intake of calcium and vitamin D in our cases or to the shorter duration of the disease, or both.

Dwarfism is found in children with renal rickets but is absent when the renal hyperparathyroidism begins after the adolescent growth period. There was no retardation of growth in the 2 infants studied. The suggestion is tentatively offered that the dwarfism is the result of the epiphysial changes due to vitamin D deficiency rather than of the hyperparathyroidism itself.

CALCIFICATION OF ARTERIES AND DEPOSITS OF CALCIUM IN BOTH LUNGS IN AN INFANT

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There have been occasional reports of extensive calcification of the arteries in infants, but the condition is still sufficiently rare to be of interest. Along with calcification of the arteries, in the case here reported there was the additional feature of widespread calcium deposition in the lungs. The patient was observed only during life, and therefore the diagnoses were made from information obtained from the history, physical examination, laboratory procedures and roentgen ray studies.

REPORT OF A CASE

A girl 1 year of age was brought to Vanderbilt University Hospital on Nov. 8, 1940 because of failure to gain weight and marked anemia. The history revealed that the baby had been born at full term, weighing 6 pounds 4 ounces (2,835 Gm.). For the first hour following her birth she had "grunted" with each breath, but her condition immediately after this was said to have been satisfactory. After one week of breast feeding she had been weaned because of frequent watery stools, and a dilute whole milk and corn syrup formula had been offered every two hours. When she was 4 months of age the interval between feedings had been increased to four hours. After she was 1 month of age she had received the juice of one orange daily; after the age of 4 months she had received ¼ teaspoon of cod liver oil three times daily for three months; then she had been given enough cod liver oil concentrate to furnish her with 1,000 U. S. P. units of vitamin D and 10,000 U. S. P. units of vitamin A daily. Her gain in weight was slow but fairly uniform, and at 7 months of age she was said to have weighed 13 pounds (5,897 Gm.). She had been able to sit alone for a short time at the age of 8 months but had never been able to stand. No teeth had erupted before her admissioin to the hospital. Since birth constipation had been persistent and had been relieved by enemas and laxatives. For several weeks before she came to the hospital, regular doses of liquid petrolatum had been administered.

The family history contributed little. One sibling had died of pneumonia on the fourth day of life, and another sibling was in good health. The patient was the result of the third pregnancy. The father's sister had died of pulmonary tuberculosis before the birth of the patient.

At the age of 7 months the patient had a febrile illness lasting for three days, terminating with a generalized rash and disappearance of fever. At about this

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time cereal and vegetables were offered and were taken fairly well. One month later she had an acute illness that was said to be a "chest infection," accompanied by a temperature of 104 F. for four days. After this she refused to eat cereal and vegetables, and within a few weeks she was taking only 1 to 2 ounces (30 to 60 cc.) of formula at a feeding. The same amount was ingested when the feeding interval was shortened from four hours to two hours. Her attending physician discovered that she was anemic and prescribed a liver and iron preparation. Small amounts of meat and crackers were eaten, but with the exception of her formula all other foods were refused after the age of 8 months. After the onset of her first febrile illness, at the age of 7 months, loss of weight was progressive, and at the time of her admission to the hospital she weighed only 9 pounds (4,082 Gm.).

On admission the patient was found to be small for her age (fig. 1), extremely malnourished and pale. Her skin was dry, inelastic and loose, and there was no eruption. The anterior fontanel was almost closed. The buccal mucous membrane was pale; there were no teeth. There were no palpable masses in the neck. The

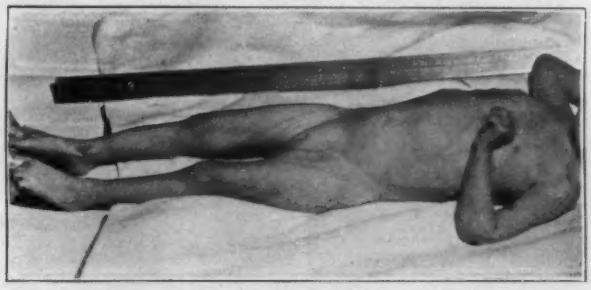

Fig. 1.—One year old infant with calcification of the arteries and deposits of calcium in both lungs (length, 68.4 cm.; occipitofrontal circumference of the head, 38.3 cm.; circumference of the chest, 35.4 cm.).

thorax appeared to be bilaterally symmetric, and expansion of the two sides was equal. The ribs were prominent. The heart was not enlarged to percussion; there was a soft systolic murmur with greatest intensity at the apex. The abdomen was sunken, and its musculature was thin. The edge of the liver extended barely below the right costal margin; the spleen and kidneys could not be palpated. The extremities were markedly emaciated. The pateller reflex was thought to be bilaterally hyperactive. The diagnoses on admission were (1) malnutrition, (2) feeding problem and (3) severe anemia, due to improper feeding.

On the day of admission the blood contained 2,400,000 erythrocytes and 30,750 leukocytes per cubic millimeter and 5.5 Gm. of hemoglobin per hundred cubic centimeters. The first specimen of urine contained a few leukocytes and gave a 1 plus reaction for albumin. Later urinalyses revealed a 1 plus reaction for albumin, a few granular casts, leukocytes and red blood cells. The Kahn reaction was negative. After admission the serum protein was found to be within normal limits on two occasions. The nonprotein nitrogen content of the blood was 176 mg. per hundred cubic centimeters: this result was checked two days later. On

different occasions the calcium content of the serum was found to be 9.2 and 10.1 mg. per hundred cubic centimeters and the inorganic phosphorus 10.5 and 12.3 mg. The p_H of the blood was 7.27, and the carbon dioxide content was 27.4 volumes per cent, with an alkali reserve of 25.7 volumes per cent. The phenolsulfonphthalein excretion by the kidneys was a little less than 3 per cent, with an appearance time of seven minutes.

Roentgenograms of the long bones showed evidence of decalcification and a marked fuzzing in outline of the trabeculations, with little epiphysial change. No shadows suggestive of calcification could be seen in the region of the kidneys.

Fig. 2.—Roentgenogram of the pelvis and femurs, showing shadows apparently due to a marked degree of calcification in the vessels of the buttocks, the perineal region and the thighs, extending up into the iliac arteries to the abdominal aorta.

There appeared to be a marked degree of calcification in the major vessels of the extremities, the iliac vessels, the abdominal aorta and the vessels of the buttocks and perineum. Roentgenograms of the lungs showed a very diffuse, extensive mottling, apparently due to calcium, some of which was arranged in linear fashion while the major portion appeared to be distributed in the parenchyma (figs. 2 and 3).

On reexamination, after the roentgenograms were studied, the sclerosed popliteal arteries were identified by palpation. On the basis of combined clinical, laboratory

and roentgen ray observations the diagnosis was calcification of arteries, deposits of calcium in the lungs, acidosis and secondary anemia.

After several small transfusions the blood picture was materially improved. On a four hour schedule the patient took 3 ounces (90 cc.) of whole milk at a feeding, regurgitating a little after each feeding. Repeated attempts to obtain the blood pressure were unsuccessful. Urine was voided infrequently and in small amounts. A cystoscopic examination was proposed, but the parents refused to grant permission for the procedure. The baby was taken from the hospital on Nov. 14, 1940, against advice. It was learned from the physician who subsequently attended her that she died two weeks after leaving the hospital. Postmortem examination was not made.

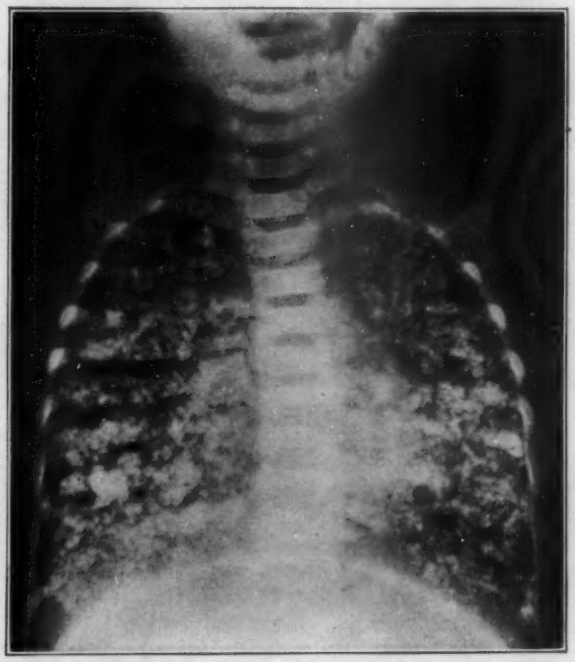

Fig. 3.—Roentgenogram of the chest showing diffuse extensive mottling throughout both lungs.

COMMENT

The coexistence of renal disease and disturbed calcium metabolism is implied by the name renal rickets. Mitchell,[1] in an extensive review of this syndrome, mentioned the frequent occurrence of sclerosis, thickening and atheromatous patches in the aorta and other blood vessels, observed at autopsy. Arterial calcification in children with renal rickets

1. Mitchell, A. G.: Nephrosclerosis (Chronic Interstitial Nephritis) in Childhood, with Special Reference to Renal Rickets, Am. J. Dis. Child **40**:345-388 (Aug.) 1930.

has also been reported by Smyth and Goldman [2] and by Shelling and Remsen.[3] Baggenstoss and Keith,[4] in a recent review of cases of calcification of the arteries in infancy, noted that in 4 of 9 cases there had been renal disease. It would seem, therefore, that disease of the kidneys sufficient to cause impairment of renal function must be considered as a frequent factor in metastatic calcification. Hyperparathyroidism,[5] either primary or secondary to renal insufficiency, and excessive amounts of vitamin D [6] have also been mentioned frequently enough to be considered as possible causes of metastatic calcification.

The case here reported must be considered purely from the clinical viewpoint, since there was no postmortem examination to furnish pathologic data. A brief summation of the positive signs gives the clinical picture of an infant whose growth and development have obviously been retarded, with poor appetite, marked anemia, impaired renal excretion, marked azotemia and phosphatemia with resultant acidosis, extensive calcification of the arteries and widespread deposits of calcium in the lungs. On the negative side, the kidneys could not be palpated, there was no roentgen ray evidence of renal calcification and there was a clearcut history of subminimal doses of vitamin D. With the age of the patient and the absence of palpable enlargement of the kidneys taken into consideration, the primary cause of this condition may well have been renal insufficiency due to congenital malformation of the urinary tract, possibly within the kidneys themselves.

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2. Smyth, F. S., and Goldman, L.: Renal Rickets with Metastatic Calcification and Parathyroid Dysfunction, Am. J. Dis. Child. **48**:596-616 (Sept.) 1934.

3. Shelling, D. H., and Remsen, D.: Renal Rickets: Report of Case Showing Four Enlarged Parathyroids and Evidence of Parathyroid Hypersecretion, Bull. Johns Hopkins Hosp. **57**:158-181 (Sept.) 1935.

4. Baggenstoss, A. H., and Keith, H. M.: Calcification of the Arteries of an Infant: Report of a Case, J. Pediat. **18**:95-102 (Jan.) 1941.

5. (*a*) Albright, F.; Drake, T. G., and Sulkowitch, H. W.: Renal Osteitis Fibrosa Cystica: Report of a Case with Discussion of Metabolic Aspects, Bull. Johns Hopkins Hosp. **60**:377-399 (June) 1937. (*b*) Albright, F.; Baird, P. C.; Cope, O., and Bloomberg, E.: Studies on the Physiology of the Parathyroid Glands: Renal Complications of Hyperparathyroidism, Am. J. M. Sc. **187**:49-65 (Jan.) 1934. (*c*) Smyth and Goldman.[2] Shelling and Remsen.[3]

6. (*a*) Thatcher, L.: Hypervitaminosis-D, with Report of Fatal Case in Child, Edinburgh M. J. **38**:457-467 (Aug.) 1931. (*b*) Ham, A. W.: Mechanism of Calcification in Heart and Aorta in Hypervitaminosis D, Arch. Path. **14**:613-626 (Nov.) 1932.

HISTOPLASMOSIS IN INFANCY

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The disease histoplasmosis, which was first described by Darling in 1906 and 1908,[1] has since been observed and reported many times. An able review by Meleney[2] appeared in 1940. Since this review and summary of 32 cases, 5 additional ones, 3 of infants[3] and 2 of adults,[4] have been reported, making the total number of cases 37. In 7 of these[5] the patients have been infants less than 15 months of age. Dodd and Tompkins[5a] were able to make the diagnosis of the disease in an infant before death. The other patients with diagnoses made during life[6] were adults.

From the Department of Pediatrics, Vanderbilt University School of Medicine, Nashville, Tenn.

1. Darling, S. T.: (*a*) A Protozoan General Infection Producing Pseudotubercles in the Lungs and Focal Necroses in the Liver, Spleen and Lymphnodes, J. A. M. A. **46**:1283 (April 28) 1906; (*b*) A Fatal Infectious Disease Resembling Kala Azar Found Among Natives of Tropical America, Arch. Int. Med. **2**:107 (Sept.) 1908; (*c*) The Morphology of the Parasite and the Lesions of Histoplasmosis, a Fatal Disease of Tropical America, J. Exper. Med. **11**:515, 1909.

2. Meleney, H. E.: Reticulo-Endothelial Cytomycosis: A Review with Mention of Thirteen Unpublished Cases, Am. J. Trop. Med. **20**:603 (July) 1940.

3. (*a*) Rhodes, P. H.; Conant, N. F., and Glesne, L. R. B.: Histoplasmosis: Report of a Case in an Infant Three Months of Age, J. Pediat. **18**:235 (Feb.) 1941. (*b*) Anderson, W. A. D.; Michelson, I. D., and Dunn, T. M.: Histoplasmosis in Infancy: Report of a Case, Am. J. Clin. Path. **11**:344 (April) 1941. (*c*) Scott, E. P.: Histoplasmosis: Report of a Case in an Infant 15 Months of Age, J. Pediat. **19**:668 (Nov.) 1941.

4. (*a*) Brown, A. E.; Havens, F. Z., and Magath, T. B.: Histoplasmosis: Report of a Case, Proc. Staff Meet., Mayo Clin. **15**:812 (Dec. 18) 1940. (*b*) Van Pernis, P. A.; Benson, M. E., and Holinger, P. H.: Specific Cutaneous Reactions with Histoplasmosis: Preliminary Report of Another Case, J. A. M. A. **117**:436 (Aug. 9) 1941.

5. (*a*) Dodd, K., and Tompkins, E.: A Case of Histoplasmosis of Darling in an Infant, Am. J. Trop. Med. **14**:127 (March) 1934. (*b*) Agress, H., and Gray, S. H.: Histoplasmosis and Reticuloendothelial Hyperplasia, Am. J. Dis. Child. **57**:573 (March) 1939. (*c*) Amolsch, A. L., and Wax, J. H.: Histoplasmosis in Infancy: Report of a Case, Am. J. Path. **15**:477 (July) 1939. (*d*) Shaffer, F. J.; Shaul, J. F., and Mitchell, R. H.: Histoplasmosis of Darling: Fourth Case to Be Reported in the United States, J. A. M. A. **113**:484 (Aug. 5) 1939. (*e*) Footnote 3.

6. (*a*) Mantell, F. J.; Troy, T. S., and Kendall, W. S., cited by Meleney.[2] (*b*) Strong, R. P.: A Study of Some Tropical Ulcerations of the Skin with Particular Reference to Their Etiology, Philippine J. Sc. **1**:91 (Jan.) 1906. (*c*) Hansmann,

(Footnote continued on next page)

The patient here described is the eighth infant to be reported on and the second one in whose case a diagnosis of histoplasmosis was made before death.

REPORT OF A CASE

The patient, a white girl, was born on Oct. 29, 1940, at full term, by normal delivery. An evaporated milk formula was given, in addition to breast milk after the age of 10 days, and after two months the breast feeding was discontinued. She was given adequate amounts of percomorph liver oil and orange juice. Her gain in weight was steady, and she was thought to be in good health until about one week before her admission to the hospital. At that time her parents noticed that she was irritable and slept less than usual. For about one month she had been rolling her head from side to side, but no particular significance had been attached to this. Five days before admission her temperature was 103 F. by rectum. After this a thermometer was not used, but it was thought that she felt very warm at times. There had been no vomiting and no change in the character, frequency or number of stools. She was taken to a physician, who found that she had an enlarged liver, an enlarged spleen, rather marked anemia and leukopenia, with a slight predominance of lymphocytes and a few unclassified cells. Because of these observations the patient was hospitalized on April 10, 1941. The family history contributed no relevant facts.

Physical examination revealed a well developed and well nourished infant of 5 months, with a temperature of 102.2 F. (rectal), a pulse rate of 146 and a respiratory rate of 42. She did not appear to be acutely ill but acted as though she suffered some pain when she was lifted or turned over. There was moderate pallor of the skin and mucous membranes. The submaxillary and inguinal lymph nodes were slightly enlarged and were discrete. The periphery of the left ear drum was injected; the right drum gave no light reflex, but there was no bulging. The pharynx was mildly hyperemic, and a yellow mucoid discharge clung to the posterior pharyngeal wall. There were slight impairment of resonance and suppression of breath sounds immediately below the right scapula, but no rales could be heard. The abdomen appeared large, rounded and symmetric. The spleen was enlarged, smooth and apparently not tender; its lower border extended 3 fingerbreadths below the left costal margin. The smooth edge of the liver was felt 3 fingerbreadths below the right costal margin. There was a small umbilical defect.

It was thought that the infant had bilateral acute catarrhal otitis media, possible bronchopneumonia on the right side and anemia, secondary to infection.

The results of laboratory examination on admission were as follows: the Kahn reaction was negative. The urine (uncentrifuged) showed 1 to 3 leukocytes per high power field. The blood contained 4,850,000 erythrocytes and 7,650 leukocytes per cubic millimeter and 8.4 Gm. of hemoglobin per hundred cubic centimeters. A differential count showed 44 per cent polymorphonuclear leukocytes, of which 35 per cent were segmented forms, 1 per cent eosinophils, 52 per

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G. H., and Schenken, J. R.: A Unique Infection in Man Caused by a New Yeast-Like Organism, a Pathogenic Member of the Genus Sepedonium, Am. J. Path. **10**:731 (Nov.) 1934. (*d*) Reid, J. D.; Scherer, J. H., and Irving, H.: Systematic Histoplasmosis in the United States, Science **91**:264 (March 15) 1940. (*e*) Footnote 4.

cent lymphocytes and 3 per cent unclassified cells. There were 721,000 platelets per cubic millimeter. The intradermal injection of 0.1 mg. and of 1 mg. of old tuberculin elicited no reaction.

Cultures of blood made on the day of admission and on the tenth day after admission were discarded as sterile after five days' observation. A culture of urine made on the fifth day was sterile. Two thick drop preparations and repeated thin smear preparations of the blood showed no parasites. Agglutinations for Bacillus typhosus, Bacillus paratyphosus A, Bacillus paratyphosus B, Brucella abortus, Brucella melitensis, Brucella suis and heterophile antibodies all gave negative results on two occasions.

Examination of blood stained supravitally contributed nothing of importance. On the twentieth day after admission, sternal puncture was performed, and a

Fig. 1.—Smear of sternal marrow (Wright's stain; × 1,800), showing a young mononuclear cell containing basophilic ovoid bodies surrounded by clear zones (arrows).

supravital preparation of a portion of the marrow was examined.[7] During this examination several free forms which appeared to be yeast cells were discovered, but they could not be identified. From a portion of the sternal marrow smears were made and were treated with Wright's stain. In one of these smears round darkly staining bodies surrounded by clear zones were seen in several mononuclear cells. These bodies presented the appearance of Histoplasma capsulatum (fig. 1). Sternal puncture was repeated; the marrow was cultured in dextrose broth, on blood agar and on Sabouraud's dextrose agar, and all cultures were sealed. The same mediums were also used for blood cultures. Typical colonies of

7. Supravital preparations of blood and marrow were made and examined by Dr. Edna Tompkins of the Department of Anatomy, Vanderbilt University School of Medicine.

Histoplasma capsulatum, as described by De Monbreun,[8] appeared in the marrow cultures on the twelfth day and in the blood cultures after sixteen days.

On the day after admission roentgenograms of the chest showed a sharply defined shadow in the upper mediastinum just to the right of and anterior to the aorta, which was thought to be due to the thymus. Both lung fields showed a general increase in bronchovascular shadow, mostly in the bases and most marked on the right side. On the eighth day there was a little increase and on the thirtieth day a marked increase in the bronchovascular shadow, bilaterally. The mediastinal shadow (fig. 2) persisted, unchanged in size and shape.

Repeated transfusions were given, and the hemoglobin content of the blood was raised to 12 Gm. per hundred cubic centimeters, while the erythrocyte count

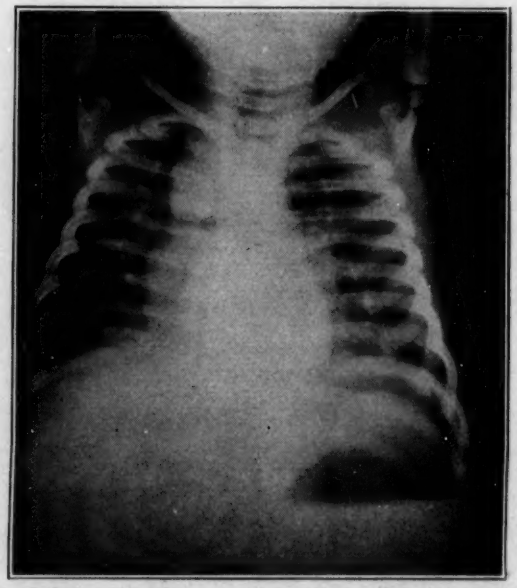

Fig. 2.—Roentgenogram of the chest (posteroanterior) showing a shadow in the right mediastinum.

remained a little above 4,000,000 per cubic millimeter. After the eighth day, it became necessary to gavage most of the feedings. Sulfathiazole (2-[paraamino-benzenesulfonamido]-thiazole), 0.25 Gm. every four hours, was given from the seventh to the fourteenth day, and quinine sulfate, 0.065 Gm. four times daily, was given from the fourteenth to the twenty-third day. After organisms were seen in the marrow, antimony therapy was started, because of the reported success of an antimony compound in the case of histoplasmosis reported by Mantell, Troy and Kendall.[6a] On the twenty-fifth day after admission 1 cc. of fuadin was given intramuscularly, followed by 1.5 cc. on the twenty-sixth day and 1 cc. on the twenty-seventh day. The leukocyte count, which had fallen to 4,000 on the eighteenth day,

8. De Monbreun, W. A.: The Cultivation and Cultural Characteristics of Darling's Histoplasma Capsulatum, Am. J. Trop. Med. **14**:93 (March) 1934.

Fig. 3.—Photograph on the twenty-eighth day after admission to the hospital, showing outlines of the lower borders of the enlarged liver and spleen.

Fig. 4.—Anterior view of the lungs, heart and enlarged thymus. The smaller right lobe of the thymus corresponds to the mediastinal shadow seen on the roentgenograms.

was 2,600 on the twenty-sixth day and 1,600 on the following day. On the twenty-seventh day the abdomen was greatly distended, respirations became labored and the baby appeared to be much worse. The liver and spleen had increased in size (fig. 3). An area of erythema, about 2 cm. in diameter, appeared on the left buttock, enlarged rapidly and became gangrenous. Areas of superficial gangrene also appeared on the abdomen and on the left thigh. On the thirtieth hospital day the patient became much worse, with more marked abdominal distention and

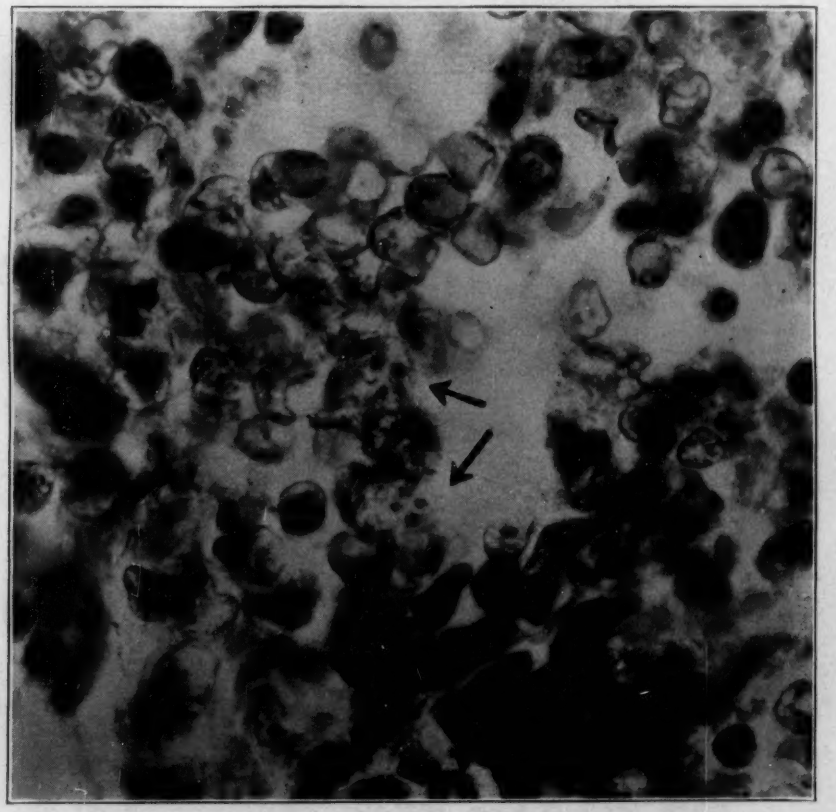

Fig. 5.—Section of the spleen (Wright's stain; × 1,800); arrows point to two groups of organisms.

labored respirations. Rales were heard over both lung fields. On the following day the bleeding time was found to be eight minutes and the platelet count was 20,000 per cubic millimeter of blood. Neostam (a pentavalent antimony preparation, stibamine glucoside), 0.02 Gm., was given intravenously. The patient's condition did not improve, and on the thirty-first day after admission to the hospital she died. Necropsy was performed two hours after death.

Numerous ecchymotic areas were seen in the skin. About 750 cc. of clear fluid was found in the peritoneal cavity, and numerous petechial hemorrhages were

seen beneath the serosa of the ileum and colon. Two firm slightly elevated opaque patches were seen in the pleura, one in the upper lobe of the right lung and the other in the lower lobe of the left lung. The bases of the lungs felt nodular. Small slightly elevated grayish white areas extended from the hilus of the right lung toward the periphery. The bronchial nodes were markedly enlarged, especially on the right side. The thymus was firm and nodular and extended about half way to the diaphragm (fig. 4). In the intestinal tract, the lymph follicles and Peyer's patches were all hypertrophied, and there were a few granulomatous nodules occurring in Peyer's patches and in isolated areas of mucosa. The liver was considerably enlarged, and on cut section the surface had a pale brown mottled appearance, due to irregular yellowish areas scattered over it. The spleen was enlarged and flabby, and on cut section the surface was dark red. The adrenals appeared normal. The kidneys were unusually pale. There were a few petechial hemorrhages in the mucosa of the kidney pelves and in the mucosa of the bladder. The vertebral bone marrow was somewhat pale but moist.

Microscopically, there were large areas in the lungs packed with mononuclear cells and a few giant cells, whose cytoplasm was loaded with the small refractile bodies of Histoplasma capsulatum. There was fibrosis of varying degrees in these areas. Mononuclear cells and a few giant cells all filled with parasites were seen in the hilar and abdominal nodes, adrenals, liver, spleen (fig. 5), thymus, bone marrow and intestines. Acute necrosis and even caseation were found in the nodes and thymus. Slight necrosis and ulceration were seen in the granulomatous lesions in the ileum. Small areas of interstitial nephritis could be seen about vessels filled with mononuclear cells containing parasites in the cortices of the kidneys. Small areas of necrosis were also seen in the adrenals and in the bone marrow. The parasite was cultured successfully on blood agar and on Sabouraud's dextrose agar.

COMMENT

The cases of histoplasmosis of Darling occurring in infancy have been strikingly similar in mode of onset, clinical course and pathologic observations. The onset has been insidious; failure to gain weight, vomiting and diarrhea have been frequent early symptoms. Also of common early occurrence have been signs and symptoms of an infection of the upper respiratory tract, or "cold," accompanied in some cases by otitis media. Hepatomegaly and splenomegaly have been noted in all cases at the time of hospitalization. Anemia has been present in all cases and leukopenia in all but 1.[5a] Enlargement of the superficial lymph nodes has not been generalized or prominent. Cutaneous lesions have been frequent, tending to be ulcerative if occurring early and hemorrhagic or purpuric if occurring late in the disease. Clinical signs or roentgen ray evidence of bronchial or pulmonary infiltration have been reported in all but 1 case.[5d] Urinary observations have consisted of changes usually found in any febrile disease. Necropsy has revealed invasion of the bone marrow, visceral chains of lymph nodes, the lungs, the spleen, the liver and frequently the ileum by large numbers of parasites. Other organs have been found to harbor varying numbers of

the refractile bodies. In small blood vessels and lymph spaces, endothelial cells and large mononuclear cells containing the organisms are commonly found.

Whenever such a clinical picture is seen, the diagnosis of histoplasmosis should be seriously entertained as soon as the more common causes have been eliminated. A persistent effort to demonstrate the parasites should then be made. Because of the usual leukopenia and because of the presence of the parasites in mononuclear cells, which comprise only a small percentage of the circulating leukocytes, the difficulty in making a diagnosis by examining blood smears is readily apparent. It is interesting to note that the 1 case in which a diagnosis was made from blood smears was the only case in which there was a leukocytosis.[5a] In the case here reported the organisms were not found in dehemoglobinized thick drop preparations. Culture of 8 to 10 cc. of blood in dextrose broth should reveal the presence of the parasites, but growth is slow, requiring several weeks before identification is possible. Stained smears from sternal marrow offer a better chance for relatively rapid diagnosis, since they display a much larger number of leukocytes than do blood smears. Diligent search of many smears should be made before this procedure is abandoned as fruitless. Cultures on blood agar, on Sabouraud's dextrose agar and in dextrose broth should also be made from some of the marrow. A specific cutaneous reaction to filtrates of broth cultures of the fungus was recently described by Van Pernis, Benson and Holinger.[4b] Because of the gravity of the disease and the inevitable mortality that has attended it in infants, there is ample justification for splenic puncture if more benign measures fail. The spleen has been enlarged fairly early in all cases, and it is reasonable to believe that the splenic pulp is invaded early. Stained smears of material aspirated from the enlarged spleen should offer the most certain means of diagnosis. Cultures should also be made from a portion of the material obtained at the same time smears are examined.

Treatment of the disease still remains in doubt, although 2 adult patients have been treated with some degree of success. One patient,[6b] presenting a cutaneous lesion, was treated by curettage and antiseptic dressings. After four months there was no evidence of the infection. The other[6a] had a generalized febrile illness and was treated with neostam (stibamine glucoside). Although this patient showed some immediate improvement, a recent report[9] indicates that he cannot be regarded as cured. Since the disease has been manifested in infants as a generalized infection, chemotherapy would seem to offer the most promise. In this case, therapy with an antimony preparation was

9. Personal communication from Dr. C. L. Wood, Acting Medical Director, Veterans Administration, Washington, D. C.

started only six days before the patient's death, when invasion by the parasites was already so widespread that little, if any, result could be expected from treatment. Although neostam was thought to be of benefit in 1 case, antimony and potassium tartrate had no apparent effect in the case reported by Brown, Havens and Magath.[4a] Multiple transfusions have afforded little more than temporary improvement. Ionized copper, large doses of potassium iodide and roentgen ray therapy were all employed without success by Hansmann and Schenken.[6c] Sulfanilamide proved ineffective in 2 infants and in 1 adult.[10] In the present case sulfathiazole administered during the third week after the onset of symptoms was also ineffective. There was no response to quinine sulfate. Other measures, mainly palliative, have failed to give even symptomatic relief.

SUMMARY

A case of histoplasmosis of Darling in a girl 5½ months of age is reported.

A correct diagnosis was made from smears of marrow obtained by sternal puncture eleven days before death.

It is suggested that for any infant having an illness of insidious onset with pyrexia, vague gastrointestinal disturbances, symptoms of an infection of the respiratory tract, anemia, leukopenia and hepatosplenomegaly, with or without cutaneous lesions, the diagnosis of histoplasmosis should be considered.

Because of the gravity of the disease and the need for earlier diagnosis if any therapy is to be of value, every effort should be made to demonstrate the typical encapsulated parasites. If repeated smears of blood and marrow fail to aid in the diagnosis, material obtained by splenic puncture should be examined and cultured.

In infants various therapeutic agents have thus far been unsuccessful, and all cases have terminated fatally.

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10. Clemens, H. H., and Barnes, M. L.: Histoplasmosis: Report of a Case, South. M. J. **33**:11 (Jan.) 1940. Footnote *3 a* and *b*.

Progress in Pediatrics

FRANCIS HOME, M.D.

THE SCOTTISH MILITARY SURGEON WHO FIRST DISCOVERED DIPHTHERIA

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Diphtheria is not a "new" disease. Known in the East for centuries, it is mentioned in the Babylonian Talmud. Aretæus the Cappadocian, who lived in Nero's reign, gave a classic firsthand account of a disease affecting the throat which may have been diphtheria. The paralysis of the palate was recognized in the sixth century by Ætius. Throat pestilences are mentioned in the Middle Ages. According to Garrison,[1] Gutierrez described *garotillo,* which was six times epidemic in Spain between 1583 and 1600, though confined to that country. In 1748 John Fothergill[2] (1712-1780) discussed a form of sore throat which was probably diphtheria. John Huxham[3] (1692-1768) was first to describe paralysis of the soft palate in connection with this disease, but he confused the condition with scarlatina. Bard,[4] in America, also wrote, somewhat vaguely, about the disease which is now called diphtheria, while Ballonius, in 1762, recognized the condition affecting the larynx and trachea.

These writers all told of the occurrence of the sore throat, sometimes in epidemic form, but none of them gave a picture of the disease as a clinical entity in all of its manifestations. The first to do that was

This article appeared also in the January 1942 issue of the *Bulletin of the Institute of the History of Medicine,* page 48.

1. Garrison, F. H.: An Introduction to the History of Medicine, ed. 4, Philadelphia, W. B. Saunders Company, 1929, p. 243.

2. Fothergill, J.: An Account of the Sore Throat Attended with Ulcers, a Disease Which Hath of Late Years Appeared in This City and Parts Adjacent, London, C. Davis, 1748.

3. Huxham, J.: A Dissertation on the Malignant Ulcerous Sore Throat, London, J. Hinton, 1777.

4. Bard, S.: An Enquiry into the Nature, Cause, and Cure, of the Angina Suffocativa, or Sore Throat Distemper, as It Is Commonly Called by the Inhabitants of This City and Colony, New York, S. Inslee & A. Car, 1771.

a Scottish military surgeon, famous in his day but now usually overlooked. He was Francis Home, later professor in the University of Edinburgh. In an essay on that subject he discussed croup, an old Scottish word for what is now called diphtheria. Even in America the term "membranous croup" is not yet entirely out of use as a designation of this disease.

Francis Home had a long career of usefulness and made not a few other important contributions to medical knowledge. Not only in his

Fig. 1.—Francis Home, M.D. (from Comrie [8]).

own land was he famous. His works were extensively used on the Continent and in the colonies, in the original Latin and English as well as in French and German translations.

Francis Home was born, probably in Edinburgh, on Nov. 17, 1719. He was the second son of James Home of Eccles, advocate and author of a number of professional and historical works. His grandfather was Sir David Home of Crossrig, Lord Crossrig, a senator of the College of Justice, as the highest Scottish court of justice is known, and his second

wife, a daughter of Francis Hepburn of Briston.[5] I have not found the name of his mother.[6]

At an early age Francis Home was apprenticed to an Edinburgh practitioner named Rattray. Even before he completed his apprenticeship Home published a small treatise on Duns Spa, a watering place near the principal town in the county of Berwick which had long enjoyed popularity among Border folk. He reasoned that the water of Duns Spa must have anthelmintic virtues, because earthworms died more quickly in it than in ordinary spring water.

Young Home was appointed a surgeon to the regiment of dragoons commanded by John Cope[7] who served with distinction from 1742 to 1748 in the British army during the War of the Austrian Succession (1740-1748). While on duty in Flanders with the British expeditionary force Home managed, during lulls in the campaign, to continue his medical studies at the University of Leyden. Leyden was then the principal educational center on the Continent, at least as far as Scottish medical students were concerned. Its ties with Edinburgh were never more intimate. Hermann Boerhaave (1668-1738), the leading physician of the age, had died only a few years before, and his celebrated successors were carrying on his work.

During his military service in Flanders surgeon Home drew up a series of regimental orders for the prevention of fevers. Many of these sanitary measures are as sound today as when he recommended them. One is particularly noteworthy. It was ordered that "the dragoons shall drink no water without it be boiled first."[8] Perhaps this is the first time this precaution was ever put into effect, in the field or elsewhere.

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5. Drummond, W.: Histories of Noble British Families, London, Wm. Pickering, 1846, vol. 2, pt. 6, p. 30. Domestic Details of Sir David Hume of Crossrig, one of the Senators of the College of Justice: April 28, MDCXCVII-January 29, MDCCVII, Edinburgh, Thomas J. Stevenson, 1843, p. 126.

6. Anderson, W.: The Scottish Nation, Edinburgh, A. Fullerton & Co., 1869, vol. 2, p. 485.

7. Sir John Cope was colonel of the Seventh Regiment of Foot and was made a Knight of the Bath for his Continental service. He was present at the battle of Dettingen, in 1743, having in the previous year been appointed to command the troops dispatched to the assistance of the queen of Hungary. He is best remembered as the leader of the Hanovarian forces opposing the Jacobites under "Bonnie Prince Charlie" in the rising of 1745. His ludicrous position at the battle of Prestonpans, where he was surprised and bewildered while half asleep, gave rise to the popular Jacobite song, "Hey, Johnnie Cope! Are ye waukin yet?".

8. Comrie, J. D.: History of Scottish Medicine, ed. 2, London, Baillière, Tyndall & Cox, 1932, vol. 1, p. 317.

The war over, Francis Home returned to Edinburgh and continued his medical studies. He received the degree of Doctor of Medicine from the University in 1750. His inaugural dissertation was entitled "De febre remittente." [9] He had seen much of remittent fever during his military service in Flanders. His dissertation became something of a standard. It was republished in 1778 in Smellie's "Thesaurus Medicus."

In 1752 he joined the Royal College of Physicians of Edinburgh, then nearing its century mark. He became president of the College before 1776. He was also an early member of the Royal Medical Society of Edinburgh.[10]

Fig. 2.—Dr. Francis Home (from Kay: Portraits of Edinburgh, 1838, vol. 1, p. 249).

In 1755 there was a great prevalence of measles in Edinburgh. The mortality was about 10 per cent.[11] In that year Home wrote a paper

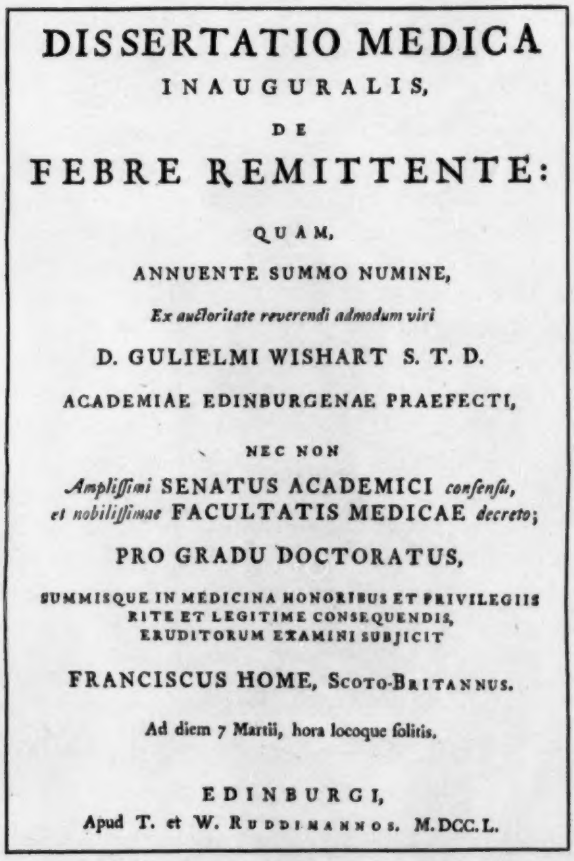
9. Home, F.: De febre remittente, Edinburgh, T. and W. Ruddiman, 1750; in Smellie, W.: Thesaurus Medicus, Edinburgh, C. Elliott et soc., 1778, vol. 1, pp. 435-464.

10. This society took its origin from a private debating society of medical students of Edinburgh in 1735. It obtained its royal charter through the efforts of Dr. Andrew Duncan (1744-1828), its president. Duncan obtained charters for three other royal institutions of the Scottish capital: the Royal Public Dispensary, the Royal Edinburgh Asylum for the Insane and the Royal Caledonian Horticultural Society (Comrie,[8] vol. 2, p. 481).

11. Comrie,[8] vol. 1, p. 319.

suggesting a method of inoculation for the prevention of the disease.[12] It was nothing more or less than the use of convalescent serum, a method considered new in the twentieth century.

His first reference to croup appeared in his "Principia Medicinæ," [13] published in 1758, in which he described a malignant angina, chiefly affecting children, which was very contagious and often attacked whole



DISSERTATIO MEDICA
INAUGURALIS,
DE
FEBRE REMITTENTE:
QUAM,
ANNUENTE SUMMO NUMINE,
Ex auctoritate reverendi admodum viri
D. GULIELMI WISHART S. T. D.
ACADEMIÆ EDINBURGENAE PRAEFECTI,
NEC NON
Amplissimi SENATUS ACADEMICI *consensu,*
et nobilissimae FACULTATIS MEDICAE *decreto;*
PRO GRADU DOCTORATUS,
SUMMISQUE IN MEDICINA HONORIBUS ET PRIVILEGIIS
RITE ET LEGITIME CONSEQUENDIS,
ERUDITORUM EXAMINI SUBJICIT
FRANCISCUS HOME, Scoto-Britannus.
Ad diem 7 Martii, hora locoque solitis.
EDINBURGI,
Apud T. et W. Ruddimannos. M.DCC.L.

Fig. 3.—Title page of Francis Home's dissertation on remittent fever, 1750. He had seen much of this disease during his military service in Flanders. This study became somethnig of a standard. It was republished in Smellie's "Thesaurus Medicus." A copy is in the Army Medical Library.

families and produced great weakness. The work in which this observation occurs was long a standard, as may be seen from the large number

12. Garrison,[1] p. 335.

13. Home, F.: Principia medicinæ, Edinburgh, G. Hamilton (and others), 1758; ed. 2, Edinburgh, A. Millar, 1762; ed. 3, Edinburgh, T. Cadell, 1770; ed. 4, Amsterdam, sump. frat. de Tournes; new ed., Venice, J. Orlandelli, 1797.

of editions through which it passed. The book was written, according to Anderson, "in correct and elegant Latin," and contained an extensive scientific history of disease. It was widely used, on the Continent as well as in Britain, as a textbook. A French edition [14] was also published.

Home's longer and better known study of croup, "An Enquiry into the Nature, Cause, and Cure of Croup," [15] was published in Edinburgh in 1765, more than half a century before the celebrated work of Pierre Bretonneau [16] (1771-1862), which provided the modern name diphtheria for the disease. The disease, an acute malady of the throat accompanied by harsh breathing and hoarse coughing, was widely prevalent in Scotland, though it had not been previously described. Home said himself that his description was the first account of the disease which, though somewhat rare in Edinburgh, was frequent in Fife, Ayrshire, Galloway and other parts of Scotland near the sea. In the "Statistical Account of Scotland," prepared by the several parish ministers in 1791, Sinclair deplored the uncommon mortality due to epidemic sore throat, the fatal results of which might have been prevented by proper care.

Squire,[17] in Reynolds' "System of Medicine," gave Home full credit for priority, calling his study "a careful and most philosophical inquiry" which showed that the symptoms depended on pathologic changes in the larynx and trachea.

Francis Home considered his monograph on croup the first systematic study of that disease. He says: [18]

> There is one disease which had entirely escaped all regular examination; and concerning which, there was little to be learned by inquiry, and still less from books; I mean the *Croup*. I never have seen anything written on this subject, except a Thesis, where the author gives us no facts; and classes it amongst the spasmodic distempers, to which it has no resemblance, either in its progress or cure. The *Catarrhus suffocativus* of *Etmuller*, tho' it resembles the Croup in many particulars, yet appears to be a very different disease in some symptoms, in the cure, and appearance after death.

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14. Home, F.: Principes de médecine, traduits du latin en françois, par M. Gastellier, auxquels on a joint un extrait d'un autre ouvrage du même auteur, intitulé: Expériences et observations de médecine, traduit de l'anglois, Paris, Vincent, 1772.

15. Home, F.: An Enquiry into the Nature, Cause, and Cure of the Croup, Edinburgh, Kincaid & Bell, 1765.

16. Bretonneau, P.: Des inflammations spéciales du tissu muqueux, et en particulier de la diphthérite, ou inflammation pelliculaire, connue sous le nom de croup, d'angine maligne, d'angine gangréneuse, etc., Paris, Crevot, 1826.

17. Squire, W., in Reynolds, J. R.: A System of Medicine, London, Macmillan & Co., 1866, vol. 1, p. 236; 1870, vol. 1, p. 70.

18. Home,[15] pp. 5-6.

PRINCIPIA

MEDICINAE.

AUCTORE

FRANCISCO HOME,

Collegii Medicorum EDINBURGI Socio.

EDINBURGI:

Apud G. HAMILTON, J. BALFOUR, & P. NEILL,
ACADEMIAE TYPOGRAPHOS.

M, DCC, LVIII.

MEDICAL

FACTS

AND

EXPERIMENTS.

By FRANCIS HOME, M. D.

Fellow of the Royal College of Phyſicians in *Edinburgh*.

LONDON:

Printed for A. MILLAR in the Strand,
And A. KINCAID and J. BELL, at Edinburgh.

MDCCLIX.

AN

INQUIRY

INTO THE

NATURE, CAUSE, and CURE

OF THE

CROUP.

By FRANCIS HOME, M. D.

His Majeſty's Phyſician, and Fellow of the Royal College
of Phyſicians in *Edinburgh*.

EDINBURGH:

Printed for A. KINCAID and J. BELL, MDCC,LXV.

[Price One Shilling.]

Fig. 4.—Title pages of three of Home's works.

Dr. *Russell*, in his Œconomy of Nature,[19] describes, in a few lines, a disease very similar to this, in most of its symptoms: But it seems not exactly the same as it was attended with ulcers about the larynx, and terminated often in a sphacelus of the lungs. Besides, had it been the same disease with our Croup, the same appearances must have occurred, upon dissection, to him as to us.

I shall, therefore, treat this disease as entirely unknown as to its nature, cause, effects, and cure; and try how far our facts will carry us towards a discovery of these.

Home then expresses wonder at the failure of others to give proper consideration to this important disease:[20]

How so singular and dangerous a disease has been totally neglected, while such attention has been paid to most others, is not the least surprising circumstance belonging to it. Its external features ought to have been sufficient to have aroused an inquisitive searcher into diseases; its internal appearances, if but once seen, must have raised, from their singularity, the strongest desire to investigate its nature. But these seem to have been more than counterbalanced by its local situation [elsewhere he says that it was common in several of the coastal counties of Scotland, but rare in Edinburgh]; the unfrequency of its appearance; the subjects which it attacked, these being generally children, and unable to give a distinct account of their complaints; the rapidity of its course; the apparent easiness of its symptoms; and their similitude to other catarrhal or peripneumoniac distempers. These seem to be sufficient reasons for its being so long undistinguished and undescribed, without laying us under any necessity of looking on it as a new disease. Probably it has existed more or less in all ages; for the same productive causes must have operated formerly, as they do at present.

He was unable to account for the comparative rarity of the disease in the Scottish capital when in the country it was not uncommon; he added that he who would study the malady must do as he had done and go to the regions where it was found. He has this to say of his having become interested in the croup:[21]

The danger of the symptoms under such apparent ease, and the singularity of its appearances after death, in the first examination, excited my curiosity. The subsequent cases were sufficient to show me its nature, tho' perhaps not to point out a certain cure. This is not always allowed to mortals. To be able, however, to distinguish it from other diseases; to discover the nature of it; to point out when it is cureable, and when not; perhaps to lay a foundation for improvement in its most desperate state; that is the design of the following pages.

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19. The "Œconomy of Nature in Acute and Chronical Diseases of the Glands" (London, J. & J. Rivington, 1755) was an English translation, made under the author's supervision, of his "De tabe glandulari, sive de usu aquæ marinæ in morbis glandularum dissertatio" (Oxford, J. Fletcher & J. & J. Rivington, 1750). The writer was Richard Russell (1700-1771), of Edinburgh.

20. Home,[15] pp. 6-7.

21: Home,[15] pp. 7-8.

To be the first author in treating a disease; to have no assistance from preceeding experience, is a situation a little uncommon in these modern times. To this cause, and to the rarity of the disease, must be imputed my not bringing it to that degree of improvement, that I could wish; and that has happened in other diseases. . . .

Home first considers the incidence of the croup, noting the susceptibility of young children:[22]

This disease appears to belong peculiarly to children; and the younger they are, after they are weaned, the more liable they seem to it. On the breast, they appear less subject to it; or, which is as probable, as they cannot tell their complaints, it is taken for some other disease. I never saw, or heard of one, above twelve years of age, affected by it. After this the body gains a strength capable of resisting the cause, or of expelling it when received. About this time, or a little after, very great changes happen in the human frame.

In his account of the clinical picture of the disease Home adopted the form of case presentations. Rather than generalize and then set forth exceptions and atypical phenomena, he allows the reader to see the patients through his eyes. The case histories are remarkably interesting and show Home to be a keen observer. The histories leave no doubt that all of the patients had diphtheria, as it is now known. Having presented case after case to illustrate the features of the disease and establish it as a definite clinical entity, the author proceeds to draw conclusions from his experience, in regard to both diagnosis and treatment. This he does in a series of "corollaries," all of which show the accuracy of his judgment. The first corollary concerns diagnosis:[23]

It seems easy, in general, to distinguish the Croup from all other diseases hitherto described. A peculiar sharp shrill voice, not easily described; a remarkable freedom from all complaints, when in imminent danger, so that they will eat a minute before they expire; a quick laborious breathing; a frequent pulse, sometimes strong at first, but always soft and weak towards the end; scarce any difficulty of deglutition, or remarkable inflammation in the *fauces;* a dull pain, often, and sometimes an external swelling in the upper part of the *trachea;* senses quite distinct to the last; and all the symptoms most rapid in their progress, characterise sufficiently this disease. I have not mentioned a cough, as that symptom is sometimes absent; and when it attends the Croup, it is not of the common kind, but more short and stiffled, and less convulsive, with little or no expectoration.

Certain other symptoms, such as "red swollen face, œdematous feet, drought, urine, sometimes with, and at other times, without a sediment, retchings, etc." are also mentioned, but the author adds that they are not so "characteristical" as those first named.

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22. Home,[15] pp. 8-9.
23. Home,[15] pp. 32-33.

With regard to differential diagnosis, the author warns against mistaking croup for "peripneumonical complaints" and severe colds. In croup the lungs are "free from any inflammation, and are not the seat of the disease." Similarly, he says, the "catarrhus suffocativus of Etmuller" is not to be mistaken for croup, since it, too, is a "peripneumony."

The disease of which Home treats bears, he found, a number of common names. On the west coast of Scotland it was called "chock" or "stuffing." In view of the characteristic shrill voice and difficult breathing, he proposed the name "suffocatio stridula" for what is vulgarly called croup.

In his second corollary Home stresses the peculiarity of the disease to a certain age and likewise its seasonal variation. In all of the cases he had observed the disease occurred between October and March. "The moist and cold weather in winter, seems to have great power in producing this disease."

The seat of the pathologic lesions is discussed in the third corollary. Though others had considered the seat of the malady to be the glottis, or even the lungs, he found that the trachea was chiefly affected:[24]

> The seat of this distemper appears to be the cavity of the wind-pipe. The place firstly, and most particularly, affected, is the upper part of the *trachea*, about an inch below the *glottis;* for in that part they complain of a dull pain, the external swelling has been observed there; and the morbid membrane we have found stretching from that place downward. The back part of the *trachea*, where there are no cartilages, seems, from the inspection of those that die of this disease, to be its first and principal seat, as this morbid membrane is often found there, when it is in no other part.

In the last corollary Home discusses the etiology of the disease. He casts aside as "fanciful erroneous opinions" the ideas expressed by "people who never gave themselves the trouble to search into the real cause of this distemper," namely, that the disease might be due to such causes as muscle spasms causing contraction of the glottis or suppuration or other inflammation of the lungs. He was more observant. He says:[25]

> The cause of this disease is a preternatural white, tough, thick membranous crust, covering, often for many inches, the inside of the *trachea*. This membrane is of so tenacious a consistence, that it can remain soaking in warm water, for many days, without dissolving. It is not attached to the parts below, but is easily separable from them, as there is always matter behind it. When it ends, the *trachea* is covered with good *pus*, or purulent *mucus;* as are, generally, the ramifications of the *bronchiæ* and vesicles, which, in some cases, were quite filled with it.

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24. Home,[15] pp. 35-36.

25. Home,[15] p. 38.

Elsewhere he compares the membrane to "the blankets of a bed that has been laid in."

For treatment Home suggested the ordinary palliative measures which were used down to the time of the introduction of intubation. However, with regard to therapy too he had far vision, for he actually suggested that tracheotomy be performed as an emergency measure to prevent the patient from suffocating. He hints in several places in his treatise that there must be some poison circulating in the blood which causes the local picture which he described.

The monograph on croup was translated into French [26] forty-four years after it was written, good evidence of its place in the medical literature of the eighteenth century. This was seventeen years before Bretonneau published his treatise.

"Medical Facts and Experiments" [27] was Home's first book in English. It is a work of 288 pages. The French translation [14] of this book, by Gastellier, in 1772, has already been mentioned. A German edition [28] appeared in 1768.

In 1768 Home was appointed professor of materia medica in the University of Edinburgh; he was the first occupant of that chair. He was, in a way, the successor of Charles Alston (1683-1760), a pupil of Boerhaave, who first taught materia medica in connection with his instruction in botany, being at the time the King's Botanist and in charge of the Royal Garden at Holyrood. Home was at the same time one of the King's Physicians for Scotland.

"Methodus materiæ medicæ," a classified syllabus of drugs for the use of students, was published by Home in 1770. It went through several editions. In it "he speculated somewhat rashly," according to Bettany,[29] "but carefully treated the physical characters and mode of administration of drugs." The last edition of this work was published in 1793.[30]

In October 1773 Home was appointed by the University of Edinburgh to teach the institutes of medicine. He continued this instruction for two years. He was not the professor of that subject, though it is not clear why he was not. The chair had been proffered to Alexander Monro Drummond, but he, having become *persona grata* to the King of

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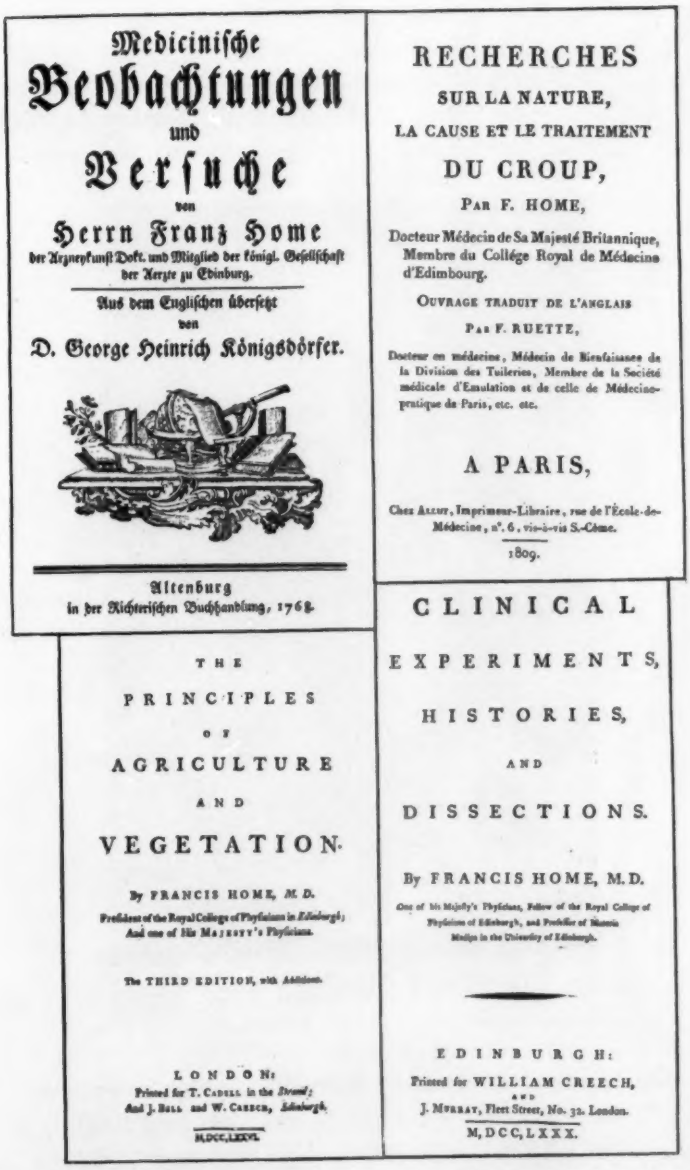
26. Home, F.: Recherches sur la nature et le traitement du croup, traduction de l'anglais par F. Ruette, Paris, Allut, 1809.

27. Home, F.: Medical Facts and Experiments, London, A. Millar, 1759.

28. Home, F.: Medicinische Beobachtungen und Versuche. Aus dem Englischen übersetzt von Georg Heinrich Königsdörfer, Altenberg, Richter, 1768.

29. Bettany, G. T., in Dictionary of National Biography, London, Smith, Elder and Co., 1891, vol. 27, p. 229.

30. Home, F.: Methodus materiæ medicæ, editio nova, Edinburgh, Bell, Bradfute & Creech, 1793.



Medicinische
Beobachtungen
und
Versuche
von
Herrn Franz Home
der Arzneykunst Dokt. und Mitglied der königl. Gesellschaft der Aerzte zu Edinburg.
Aus dem Englischen übersetzt
von
D. George Heinrich Königsdörfer.
Altenburg
in der Richterischen Buchhandlung, 1768.

RECHERCHES
SUR LA NATURE,
LA CAUSE ET LE TRAITEMENT
DU CROUP,
PAR F. HOME,
Docteur Médecin de Sa Majesté Britannique, Membre du Collége Royal de Médecine d'Edimbourg.
OUVRAGE TRADUIT DE L'ANGLAIS
PAR F. RUETTE,
Docteur en médecine, Médecin de Bienfaisance de la Division des Tuileries, Membre de la Société médicale d'Emulation et de celle de Médecine-pratique de Paris, etc. etc.
A PARIS,
Chez ALLUT, Imprimeur-Libraire, rue de l'École-de-Médecine, n°. 6, vis-à-vis S.-Côme.
1809.

THE
PRINCIPLES
OF
AGRICULTURE
AND
VEGETATION.
By FRANCIS HOME, M.D.
President of the Royal College of Physicians in Edinburgh; And one of His MAJESTY's Physicians.
The THIRD EDITION, with Additions.
LONDON:
Printed for T. CADELL in the Strand;
And J. BELL and W. CREECH, Edinburgh.
M,DCC,LXXVI.

CLINICAL
EXPERIMENTS,
HISTORIES,
AND
DISSECTIONS.
By FRANCIS HOME, M.D.
One of his Majesty's Physicians, Fellow of the Royal College of Physicians of Edinburgh, and Professor of Materia Medica in the University of Edinburgh.
EDINBURGH:
Printed for WILLIAM CREECH,
AND
J. MURRAY, Fleet Street, No. 32. London.
M, DCC, LXXX.

Fig. 5.—Title pages of the German translation of Home's "Medical Facts and Experiments," the French translation of his "Inquiry into the Nature, Cause, and Cure of Croup" and two of his publications in English.

Naples, was induced by that monarch to remain in his kingdom and to decline the offer of the town council of Edinburgh. The chair was not regularly filled until the appointment of James Gregory (1753-1821), in 1778.

Home's last book was "Clinical Experiments, Histories and Dissections," which he published in 1780.[31] In it he mentions his discovery that the sugar of diabetic urine could be fermented with yeast. This

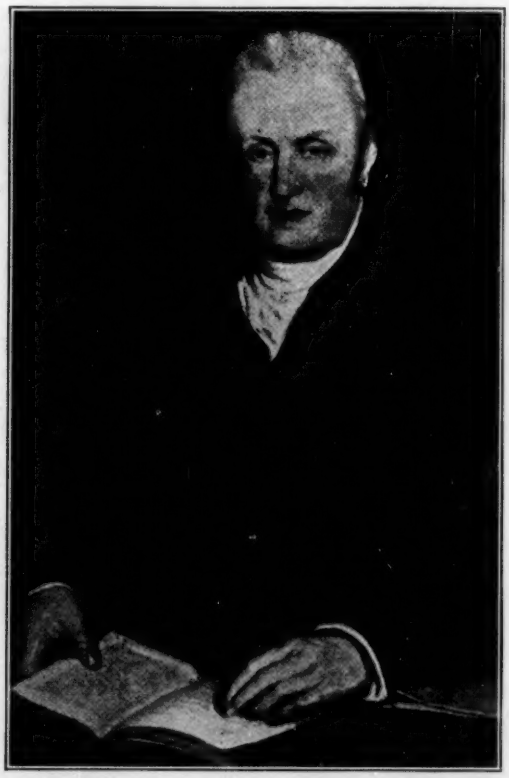


Fig. 6.—Dr. James Home (1758-1842), son of Dr. Francis Home and his successor as professor at the University of Edinburgh (from Comrie[8]).

work, too, appeared in several editions, including a translation into German.[32] By a printer's error the second and third English editions are dated MDCLXXXII and MDCLXXXIII respectively.

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31. Home, F.: Clinical Experiments, Histories and Dissections, Edinburgh, William Creach, 1780; ed. 2, London, J. Murray, 1782; ed. 3, London, J. Murray, 1783.

32. Clinische Versuche, Krankengeschichten und Leichenöffnungen. Aus dem Englischen übersetzt, Leipzig, M. G. Weidmanns Erben & Reich, 1781.

Francis Home retired in 1798 and was succeeded in the Chair of Materia Medica in the University of Edinburgh by his son, James Home (1758-1842). James Home was, says Christson,[33a] "so popular as a lecturer that his class-room was crowded every morning in the dark winter season, notwithstanding his early hour of eight a. m." He occupied the Chair of Materia Medica until 1821, when he was translated, as the expression is in Scotland, to the Chair of the Practice of Physic, as successor to James Gregory (1753-1821). The two Homes, father and son, were Tories, which added to their prestige with the Edinburgh authorities.

Francis Home was also interested in fields other than medicine. His study called "A Record of Experiments on Bleaching" [33] was awarded a payment of £100 by the Honourable Board of Trustees for the Improvement of Fisheries and Manufactures in North Britain and was considered to have been of great benefit to industry. It was published in 1756 by order of the Board and subsequently was translated into French and German.

In 1776 his treatise entitled "Principles of Agriculture and Vegetation" [34] was awarded a gold medal by the Edinburgh Society for the Improvement of Arts and Manufactures. In it he endeavored to introduce chemistry into agriculture. This book is thought to have been the first to show that plants take up nutrient matter from the air. A third edition was brought out in 1776, and there were a French translation in 1761 (Paris) and a German translation in 1779 (Berlin). The work was long considered the most scientific account of the subject. As a result of the success of the publication Dr. Home was appointed first professor of agriculture at the University of Edinburgh. He was past 71 years of age.

He died in Edinburgh on Feb. 15, 1813.

Perhaps it is only among the sons of a country like Scotland, where pedigrees are said to be long and purses short, that the distant ties of blood connecting the subject of this memoir and the writer thereof would be traced. By actual count the one is the eighth cousin five times removed of the other! They were born one hundred and seventy years apart, and their nearest ancestor in common perished at the battle of Flodden, in 1513! The name Home is pronounced Hume, as it is also often spelled.

32a. Life of Sir Robert Christson, Bart., Edinburgh, 1885, vol. 1, pp. 76-78.

33. Home, F.: A Record of Experiments on Bleaching, Edinburgh, published by the Board of Trustees for the Improvement of Fisheries and Manufacturers in North Britain, 1756.

34. Home, F.: Principles of Agriculture and Vegetation, London, T. Cadell, 1757.

DEVELOPMENTAL ENAMEL DEFECTS

CLINICAL DESCRIPTIONS AND CLASSIFICATION

BERT G. ANDERSON, D.D.S.
NEW HAVEN, CONN.

The abnormality of the teeth known as hypoplasia of the enamel is to dental practitioners and pediatricians a well recognized clinical entity and has been the subject of considerable dental research. Although the condition was previously described in the literature under such names as atrophy, erosion and honeycombed teeth, the term hypoplasia was first employed by Zsigmondy [1] (1893). Black [2] (1908) described various types of defects of the enamel under the heading "dystrophies of the teeth." Berg [3] (1919) reported the occurrence of hypoplasia of the enamel in 56.6 per cent of a group of children with cataracts. He graded the defect into four types according to its severity and stated that it is generally believed to be caused by rachitis, congenital syphilis or childhod diseases which disturb the general metabolism. The Medical Research Council of London [4] (1925) reported on the incidence of hypoplasia of the enamel in a series of children and proposed a classification. Hess [5] (1929) reported the dental observations in a study concerned with rickets, osteomalacia and tetany. In his chapter on hypoplasia of the enamel Partsch [6] (1932) drew attention to three commonly observed forms of this defect. Calteux [7] (1934) differentiated in more detail

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From the Department of Surgery, Yale University School of Medicine.

Read at a meeting of the Southern Dental Association, Chattanooga, Tenn., Feb. 5, 1940.

1. Zsigmondy, O.: Beiträge zur Kenntnis der Entstehungsursachen der hypoplastischen Schmelzdefekte, Tr. World's Columbian Dent. Cong. **1**:48-67, 1894.

2. Black, G. V.: Operative Dentistry, Chicago, Medico-Dental Publishing Company, 1908, chap. 1.

3. Berg, F.: Hypoplasias of Enamel and Clouding of the Crystalline Lens, Odont. tidskr., 1919, vol. 28, no. 2.

4. Report of the Committee for the Investigation of Dental Diseases: II. The Incidence of Dental Caries in Children, Medical Research Council, Special Report Series, no. 97, London, His Majesty's Stationery Office, 1925, p. 11.

5. Hess, A. F.: Rickets Including Osteomalacia and Tetany, Philadelphia, Lea & Febiger, 1929, p. 229.

6. Partsch, C.: Handbuch der Zahnheilkunde, Munich, J. F. Bergmann, 1932, vol. 1, p. 68.

7. Calteux, J. P.: Die Schmelzhypoplasie, Thesis, Bonn, 1933, Leipzig, Georg Thieme, 1934.

the various types of deformity observed in a group of school children. For the most part writers have dealt with defects in the enamel which are here considered to be usually associated with rickets. These they have classified into separate groups. Good illustrative material has been wanting as a rule. A classification of mottled enamel based on the severity of the condition was also proposed by Dean [8] (1934). According to him, microscopic confluent pitting is found in severe forms of mottled enamel.

Dorland's dictionary [9] defined hypoplasia as "defective or incomplete formation." Karsner [10] (1938) stated:

> Atrophy is an acquired reduction in size of an organ or cell. It implies that the cell or organ or tissue has reached mature size before the reduction occurs, and is not to be confused with developmental defects such as agenesia, aplasia and hypoplasia. Agenesia usually signifies complete absence of an organ or tissue, due to some fault or deficiency of anlage. Aplasia refers to a failure of development to anything like mature size, although a mass of tissue, often merely of connective tissue, is found in the position of the organ. Hypoplasia indicates a failure of full development, the organ being well formed but congenitally small.

Karsner's definition will be accepted for this presentation.

The main purpose of this paper is to present a clinical classification of developmental defects of the enamel which may serve to further the organization of present knowledge of these deformities. Although gross changes in the dentine were also observed in a number of instances, only the enamel is considered in these descriptions. The deciduous teeth are not included in this classification, owing to insufficient data concerning these structures.

The material used here has been made available through the cooperation of the Peiping Union Medical College and Yale University School of Medicine.

Before proceeding with descriptions of the structure of deformed enamel it is well to consider briefly the gross appearance of normal enamel. There is, of course, a certain irregularity of form and variation in this structure. Unworn teeth may show an irregular number of mamelons, or cusps, and the incisal edges, cusps, ridges, pits or grooves may be more irregularly formed in some teeth than in others. The

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8. Dean, H. T.: Classification of Mottled Enamel Diagnosis, J. Am. Dent. A. **21**:1421-1426, 1934.

9. Dorland, W. A. N.: The American Illustrated Medical Dictionary, ed. 16, Philadelphia, W. B. Saunders Company, 1932.

10. Karsner, T. H.: Human Pathology, Philadelphia, W. B. Saunders Company, 1931, p. 587.

surface of the enamel may show a variable number of more or less indistinct waves, and the outcropping of the incremental lines (imbrication lines of Pickerill,[11] 1914) may be exaggerated. The whole form of the crown also varies greatly in size and in thickness of the enamel. Since there is no satisfactory standard for the form of a tooth, it is difficult to establish a borderline between normal and abnormal varieties, and therefore it is necessary to keep in mind, for purposes of comprison, a moderately well formed crown with a moderately smooth surface.

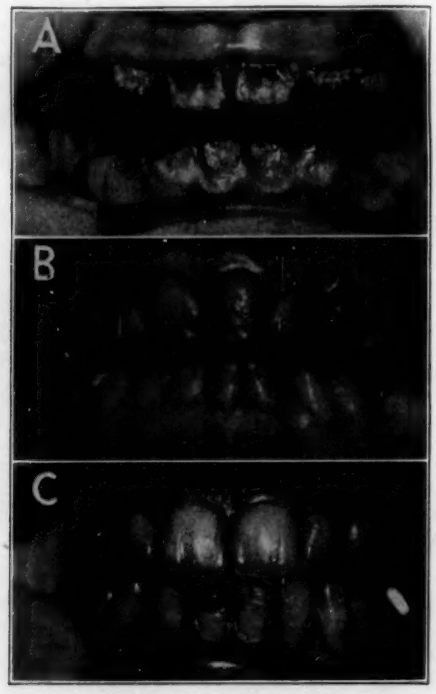


Fig. 1.—Photographs (natural size) showing (*A*) agenesia, a complete failure of formation of the enamel, (*B*) dental aplasia, with a substitute substance for the enamel, and (*C*) injury spots of the enamel following trauma and infection.

Agenesia (fig. 1 *A*), or complete failure of enamel formation, has been clinically observed by the author in 3 persons. In these the surfaces of sensitive yellowish brown or darkly stained dentine were exposed in the oral cavity. The crowns were lacking the normal form and contour of the enamel covering, which resulted in severe traumatic injury to the gingivae from impaction of food directly into the crevicular

11. Pickerill, H. P.: Prevention of Dental Caries, ed. 2, London, Baillière, Tindall & Cox, 1914, p. 64.

space. There was also a considerable amount of accumulation of food and other debris on the teeth. These patients presented marked gingivitis, with strikingly little caries, and the exposed dentine was not highly sensitive to the ordinary stimuli of the oral cavity. The general physical examinations of these patients yielded nothing that could be considered relevant to the dental defect.

Aplasia (fig. 1 *B*) has been observed in 1 patient, a man 28 years of age, who presented himself for treatment of an aching maxillary first permanent molar. This tooth was extracted and sectioned for histologic study. The coronal portion was covered with a thin coating (approximately one-third the thickness of normal enamel) of a structureless substance which, except for its yellowish brown color, thinness and imperfect contour, seemed to afford a fairly satisfactory substitute for the enamel. On both gross and histologic examination this substance was seen to be homogeneous and amorphous. All the permanent teeth were present and were coated with this hard, glazed substitute for enamel. All had roughness of the crowns in the incisal and occlusal regions.

Injury spots (fig. 1 *C*) are defects of the enamel following trauma with localized infection. In 4 patients there was a definite history of trauma to certain deciduous teeth with signs of periodontal inflammation over a period of several weeks following this injury. The resultant defects are localized to areas of enamel on those permanent teeth which replace the traumatized deciduous ones. These are characterized grossly by brownish stained depressions occurring in those portions of the enamel that were calcifying at the time of injury.

Opaque enamel (fig. 2) has been described by Black under the two headings "white spots" and "white enamel." This defect frequently occurs in cloudlike spots (fig. 2 A) which resemble the "moon spots" that are commonly seen in the human nail. They may be white or yellowish brown. The normal external form and contour of the enamel are maintained and present a smooth, glazed surface. The defect may be confined to one or to a very few teeth. When more than one tooth is affected, the condition tends to occur within horizontal zones over the surface of the crown and to involve the teeth symmetrically. There is a marked tendency for the lower anterior teeth to escape this damage. In a series of twenty-four dentitions having opaque spots on the upper anterior teeth, only two lower incisors were affected. The opaque defect of the enamel may occur in lines or bands distributed horizontally over the surface of the tooth and symmetrically over the dentition (fig. 2 *B*). The white enamel described by Black tends to affect the whole dentition generally. Differentiation of the various types of opaque enamel, including the chalky enamel of the mottled type, is often difficult. According

to Gottlieb [12] (1920), "The different forms of defective calcification especially chalky enamel, are preliminary phases of enamel hypoplasia."

Mottled enamel (fig. 3) is a defect characterized, as a rule, by a marked defacement of the teeth. Although the normal form and contour of the crown are maintained, the teeth erupt with defective enamel which often becomes extremely badly defaced with a brown stain, especially on those surfaces that are exposed to view when the lips are in a relaxed position. The primary defect is a chalky-looking but as a rule smoothly

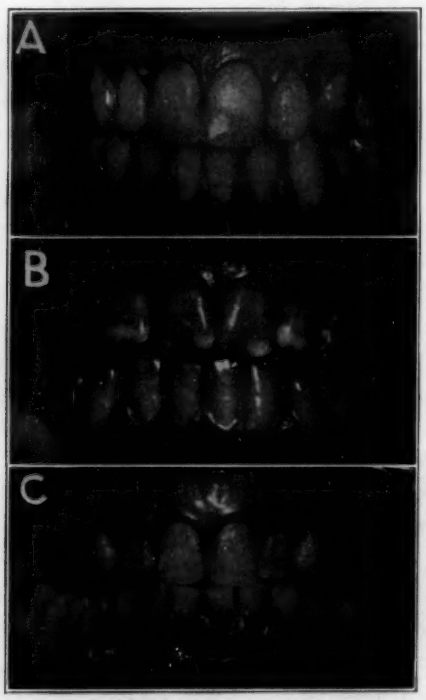


Fig. 2.—Photographs (natural size) showing three varieties of opaque enamel and its distribution over the labial surfaces of the anterior teeth.

glazed opaque enamel. According to Dean,[8] there may be a pitting of the surface. Smith [13] (1933) reported the cause of this condition to be an excess of fluorine in the drinking water. Although the staining is posteruptive and is confined to certain parts of the anterior teeth, the preeruptive primary defect may be uniformly distributed over the entire enamel of the whole dentition (fig. 3*C*) or may be found irregularly

12. Gottlieb, B.: Rachitis and Enamel Hypoplasia, Dent. Cosmos **62**:1209 and 1316, 1920.

13. Smith, M. C., and Lantz, E. M.: Experimental Production of Mottled Enamel, Technical Bulletin 45, University of Arizona, 1933.

distributed in spots or patches on the enamel (fig. 3 *A*). There is no strong tendency for this defect to follow a zonal distribution as do some of the other defects of the enamel. The lower anterior teeth are not so frequently or so markedly affected as the upper anterior ones. This defect is found endemically in various parts of the world. In 1932 I [14] described an endemic center in North China where the condition was present in all persons examined and mostly in severe form. The accompanying illustrations are from this region.

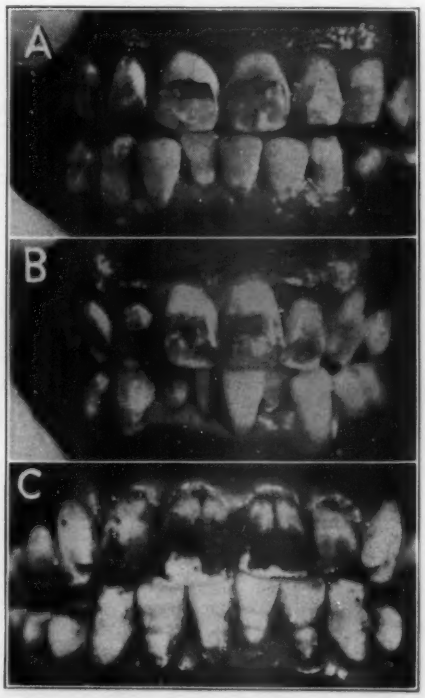


Fig. 3.—Photographs (natural size) showing three grades of mottled enamel and its distribution over the labial surfaces of the anterior teeth.

Rachitic enamel (fig. 4) is so designated because of its association with rickets. Eliot, Souther, Anderson and Arnim [15] (1934) found this defect of the enamel in 34 per cent of a group of children with moderate and severe rickets. The condition is characterized by thinning, pitting and grooving of the enamel. The defect follows strikingly a zonal

14. Anderson, B. G.: An Endemic Center of Mottled Enamel in China, J. Dent. Research **12**:591, 1932.

15. Eliot, M. M.; Souther, S. P.; Anderson, B. G., and Arnim, S. S.: A Study of the Teeth of a Group of School Children Previously Examined for Rickets, Am. J. Dis. Child. **48**:713-729 (Oct.) 1934.

distribution over the individual tooth and a bilateral symmetry over the dentition as a whole. It involves especially those parts of the crowns of the teeth that were calcifying at the time of the rachitic activity. The crowns of the permanent incisors, cuspids and first molars are the ones commonly affected. Figure 4 *A* is a photograph of a dentition in which the incisal portions of the anterior teeth are seen to be badly deformed, indicating that the injury occurred while this part of the enamel was calcifying. The rest of each damaged tooth completed its development normally. In figure 4 *B* are seen anterior teeth in which the incisal edges

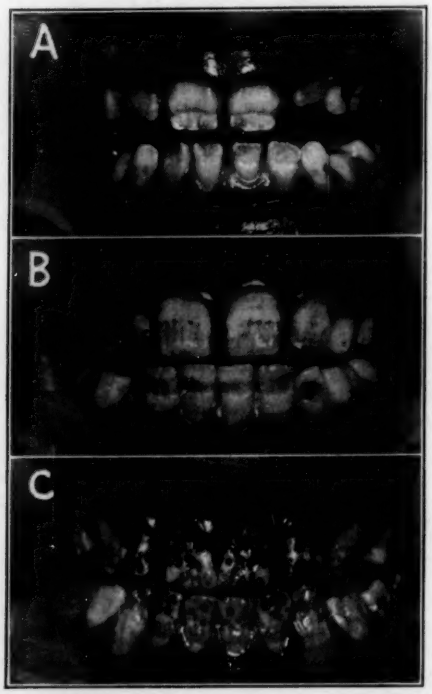


Fig. 4.—Photographs (natural size) showing three types of rachitic enamel and its distribution over the labial surfaces of the anterior teeth.

have escaped injury while a zone between this portion and the cervical line shows marked changes. Figure 4 *C* shows enamel with severe intermittent damage over its entire surface. This condition manifests itself in both the gross and the histologic structure of the tooth and usually constitutes a severe dental deformity.

Syphilitic enamel (fig. 5) is a defect associated with congenital syphilis and commonly found in groups of teeth corresponding to those affected in rickets. The examples shown in figure 5 are from a series

of dentitions I described in 1939[16] and present varying degrees of severity of this condition. There is a tendency toward a symmetric distribution almost equal to that seen in rachitic dentitions. In rickets the defect in an individual tooth is limited to zonal distribution on the crown involving that portion of the enamel that was calcifying at the time of injury. The rest of the crown escapes permanent damage and is normally developed before and after the injury. In congenital syphilis, on the other hand, the entire enamel is more likely to be involved in the malformation, since the whole tooth tends to be undersized and dwarfed.

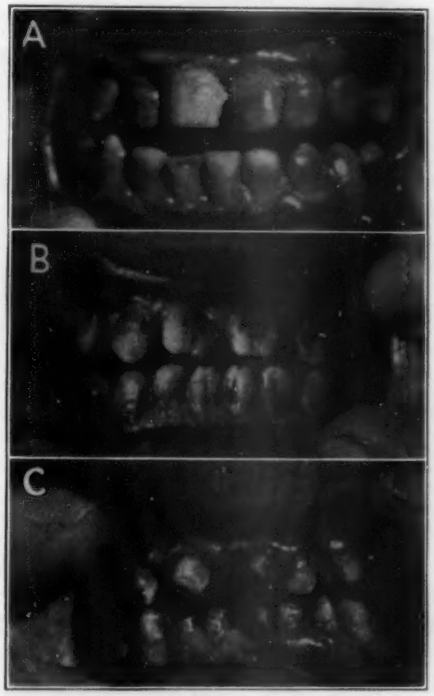


Fig. 5.—Photographs (natural size) showing the involvement of the anterior teeth and three grades of enamel defects associated with congenital syphilis.

The tooth, however, may be covered with smooth, normal-appearing enamel. There is a marked tendency, pointed out by Hutchinson[17] (1861), toward failure of development of the central mamelons in the permanent incisors in congenital syphilis.

16. Anderson, B. G.: Dental Defects in Congenital Syphilis, Am. J. Dis. Child. **57**:52-57, (Jan.) 1939.

17. Hutchinson, J.: Hereditosyphilitic Struma, and on the Teeth as a Means of Diagnosis, Brit. M. J. **1**:515-519, 1861.

Increasing experience with these types of dental defects indicates that there are some which do not readily fall into any one of the sections of this classification. Patients with such conditions, however, are relatively few.

The defects of the enamel described here do not conform to Karsner's definition of hypoplasia. Most of them, at least, seem to follow injury to the forming enamel or to the formative enamel organ by some agent external to it. The defects probably do not arise owing to an inherent

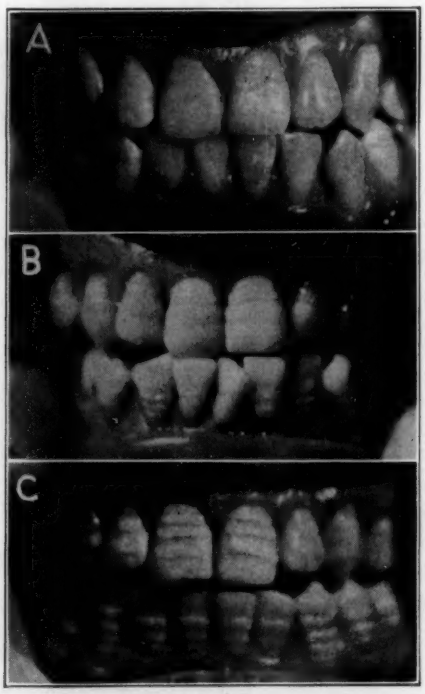


Fig. 6.—Photographs (natural size) showing three grades of corrugated enamel and its distribution over the labial surfaces of the anterior teeth.

failure of growth of the developing structure itself. They probably should be considered to be the result of damage inflicted on and permanently recorded in the developing enamel.

No reference to hyperplasia of the enamel has been found in the literature. Dorland defines hyperplasia as "the abnormal multiplication or increase in the number of tissue elements." According to Karsner, "Hyperplasia is a truly progressive change in that it represents an increase in the number of cells in a part, usually as the result of inflammation or irritation." In his chapter on dystrophies of the teeth, Black published a photograph illustrating what he termed "wrinkled or

corrugated enamel." Karnosh [18] (1926) discussed corrugated enamel and also published a photograph showing the condition "recurring annually from the second to the eighth year, with intercurrent infections (measles and whooping cough)." Figure 6 illustrates varying degrees of severity of the defect. I observed this condition developed to a striking degree in a Chinese man aged 20 (fig. 6*C*) and to a lesser degree in a Chinese woman aged 30 (fig. 6*B*). In both their cases complete medical histories and thorough general physical examinations showed no essential abnormalities. It will be noted that the waves of enamel on the dentitions correspond to the yearly progression of calcification of the crown. In a sample group of 100 Chinese persons this condition was found to be present in every person to a slight degree, varying from that shown in figure 6*A*. The condition is usually rather inconspicuous and can be easily overlooked during an ordinary dental examination. Yet this wavy character of the surface of the enamel was found to be present particularly in the cervical portion of the teeth in each of the persons examined. The enamel had the appearance of a normal smooth and translucent structure.

If one follows this deformity in the maxillary first incisor (fig. 6*C*) from the incisal edge to the gingival line and recalls that this crown requires about five years for its complete calcification, it will be seen that after the first year of infancy, when this tooth developed normally, there is a wave corresponding approximately to each succeeding year of development. The depressed portion of the wave appears to fall below the normal contour of the enamel, while the crest rises over it. Owing to the lack of a standard of contour and thickness of the enamel, this matter must necessarily be left to a great extent to one's judgment. When the estimate of thickness of the enamel covering was made, both the patient himself and the plaster models were available. Direct inspection brought out the wavy character of the surface in much stronger relief than does the accompanying illustration. It was assumed that the regular-looking enamel of the incisal portion of the crown was a normal growth of this structure. There was then an overformation of the enamel occurring alternately with the underdevelopment. The condition suggests a widespread disorder that resulted in a lack of enamel building during one part of the year and a compensatory overgrowth during the other part, or recovery period.

18. Karnosh, L. J.: Histopathology of Syphilitic Hypoplasia of the Teeth, Arch. Dermat. & Syph. **13**:25-42 (Jan.) 1926.

News and Comment

PERSONAL NEWS

Dr. Allan M. Butler Appointed.—Dr. Allan M. Butler, of Boston, has been made medical regional director for region I (New England) for the Committee on National Defense.

DEATHS

Dr. Louise Taylor Jones died recently at McLean, Va. She was a highly respected member of the pediatric profession in Washington, D. C., before her retirement.

CORRECTION

In the article by Dr. M. Murray Peshkin entitled "Immunity to Tetanus Induced by Combined Alum-Precipitated Diphtheria and Tetanus Toxoids, Based on a Study of One Hundred and Eighty-Six Allergic Children," in the July issue (AM. J. DIS. CHILD. **62**:9, 1941), "0.05 cc." at the beginning of the twenty-sixth line on page 25 should read "0.5 cc."

Obituaries

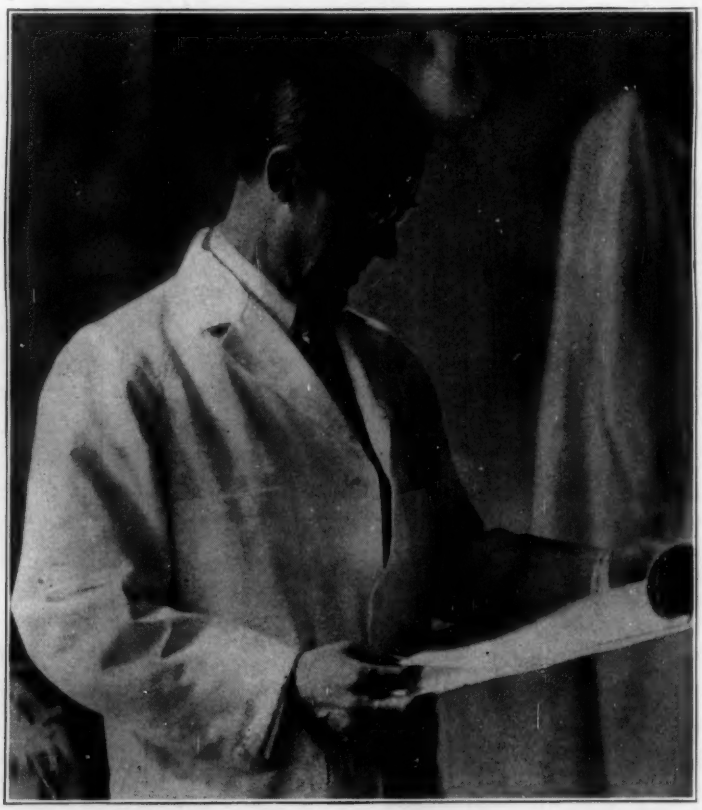
KENNETH D. BLACKFAN, M.D.
1883—1941

With the passing of Kenneth Blackfan, Thomas Morgan Rotch professor of pediatrics at Harvard Medical School, medical director of the Infants' Hospital and physician in chief at the Children's Hospital, Boston, American pediatrics has lost a leading figure who will not soon be replaced. Although not actually a pioneer in the field, he was one of that small group of teachers, investigators and students who have brought pediatrics to its prominent position among medical specialties.

Kenneth Daniel Blackfan was born in 1883 in Cambridge, N. Y., the son of Dr. H. S. Blackfan, a practicing physician of that town. He graduated from Albany Medical College in 1905. After serving under Dr. Richard M. Pearce for one year as pathologist to the Albany Hospital and bacteriologist in the Bender Laboratory, he returned to Cambridge and spent three years in the practice of medicine. Then, wishing to learn something of pediatrics, which was beginning to rise as a specialty, he went to Philadelphia, where he held an appointment as resident in charge of the St. Vincent de Paul Foundling Hospital. Here he came under the influence of Dr. David L. Edsall and Dr. Samuel M. Hamill. In 1911 he left Philadelphia, and with Dr. John Howland he and Dr. Borden Veeder went to St. Louis to develop the department of pediatrics at Washington University School of Medicine. After one year Dr. Howland returned to New York, and with him returned Dr. Blackfan, whose only plan was to stay with Dr. Howland and to learn more of his chosen field from that inspiring student and teacher. The sojourn in New York was not long. Dr. Howland became pediatrician-in-chief at the Harriet Lane Home of the Johns Hopkins Hospital, Baltimore, and Dr. Blackfan became his resident physician. Dr. Blackfan's association with Dr. Howland and the Johns Hopkins Hospital lasted eight years, during which Dr. Blackfan rose to the position of associate professor of pediatrics in the Johns Hopkins University School of Medicine. In 1920 he was called to the University of Cincinnati to become B. K. Rachford professor of pediatrics. Here his organizational ability, perspective and capacity for working and establishing cordial relations with collaborators in other departments of the medical school, as well as for commanding the deep respect of his juniors, became evident. After three years in Cincinnati, Dr. Blackfan moved to Boston

to become Thomas Morgan Rotch professor of pediatrics at Harvard Medical School. The early years at Harvard were spent in developing and establishing a firm basis for a clinic covering all phases of medical pediatrics, a clinic whose organization has been widely emulated.

Dr. Blackfan was primarily a clinician, and in the art of history taking, careful physical examination and correlation with these of appropriate laboratory data he had no peer. Yet he was alert to grasp



Kenneth D. Blackfan

1883-1941

and to apply to clinical medicine any advances in the fields of basic medical science. In the development of his clinic, attention was directed not only toward constant efforts to augment the services rendered in the care of patients but also to improve the methods of teaching medical students and nurses and to stimulate research into the cause, prevention

and cure of disease processes in infancy and childhood. Nor did his interests stop with the ill child. Improvement in the health of infants and children was sought by fostering of research into growth and development of children and into recognition of mild or slight deviations from the normal, remedy of which would result in more positive health. Dr. Blackfan was quick to recognize capabilities of his associates, and a young man with a worth while problem in the field could always secure support from Dr. Blackfan with the assurance of facilities and encouragement for his work.

Dr. Blackfan was quiet, dignified and somewhat reserved, but in his home he was friendly and most hospitable. In 1920 he married Lulie Anderson Bridges, of Louisville, Ky. He was devoted to his family and was a great companion to his son, especially during the summer vacations, which were spent on a lake near his native town of Cambridge, N. Y. He was a close observer of men as well as of patients and was endowed with a remarkable memory for details of conditions of patients, of differential diagnosis and of medical literature. He was a careful speaker and writer, weighing his words and usually striking close to the heart of any discussion.

Dr. Blackfan was an active member of the American Academy of Pediatrics, the American Pediatric Society, the Association of American Physicians and the Interurban Clinical Club and had held active membership in the American Society for Clinical Investigation. He influenced largely the formation of the Society for Pediatric Research and was an honorary member of that organization. Other honorary memberships were in the Philadelphia Pediatric Society and the Hungarian Society of Pediatrics, in addition to corresponding memberships in the British Pediatric Association and the Section for the Study of Diseases of Children of the Royal Society of Medicine.

Numerous invitations came to Dr. Blackfan to address medical societies of national and international scope. Because of his health and the demands of his position, many of these had to be refused. Dr. Blackfan's first thought was for his clinic, and if any problems presented there outside activities were of secondary importance. It was this singleness of purpose that contributed most highly to the outstanding development of his department in the medical school.

Dr. Blackfan received many honors and special commissions. He was appointed secretary general of the Fifth International Congress of Pediatrics, chairman of the Committee on Growth and Development of the White House Conference on Child Health and Protection, member of the Executive Board of the American Child Health Association, member of the International Commission on Nutrition of the Health

Section of the League of Nations, chairman of the General Advisory Committee on Maternal and Child Health under the Social Security Act, consultant to the United States Children's Bureau and member of the Council on Pharmacy and Chemistry of the American Medical Association. Not the least of the honors which Dr. Blackfan received was the respect of the members of his profession, the gratitude of the many men he befriended, the devoted loyalty of his associates and a deep sense of obligation as well as of affection from those fortunate enough to have worked under his direction and by his side.

C. F. McK.

Abstracts from Current Literature

Biochemistry; Bacteriology, and Pathology

INTERPRETATIONS OF NEUROTROPIC VIRUS CELL INCLUSIONS, WITH SPECIAL REFERENCE TO THE NEGRI BODY. CHARLES E. BLACK, J. Infect. Dis. **67**:43 (July-Aug.) 1940.

"The small Negri body containing a single internal basophilic granule, the intranuclear inclusion of poliomyelitis and the nucleoli of certain neuroglia cells particularly in small animals are identical in size, shape, contour, staining reaction and granular content.

"Nucleoli of certain neurologia cells are frequently confused with small Negri bodies, particularly in smear preparations.

"Evidence indicates that many so-called virus inclusions are actually metabolic responses of the nucleus and are not degenerative products of the cell.

"The special staining methods do not show that the Negri body is a degenerative product of the cell."

TOOMEY, Cleveland.

CONSTANT ANTISERUM OPTIMAL RATIOS OBTAINED WITH RAT PRECIPITIN. GUY P. YOUMANS and CHARLOTTE A. COLWELL, J. Infect. Dis. **67**:48 (July-Aug.) 1940.

"Precipitin production was studied in 34 rats and 5 rabbits injected with sheep serum. Antigen and antiserum dilution precipitin titers and constant antibody optimal ratios were determined.

"Rat antigen dilution titers did not exceed 1:800. Rat antiserum dilution titers were, in some cases, as high or higher than antigen dilution titers.

"Optimal ratios were obtained with 19 rat antiserums. These ratios varied from 1:0.2 to 1:32 but most of them were very low. Fifteen gave ratios less than 1:3.6 of which 8 were less than 1:1. The rate and type of flocculation obtained with rat antiserum were similar to those obtained with rabbit antiserum.

"The results in rabbits injected with sheep serum were similar to those reported by other investigators using serum antigens."

TOOMEY, Cleveland.

THE ACTION OF SULFATHIAZOLE ON THE COLON-TYPHOID-DYSENTERIAE GROUP OF ORGANISMS. RAYMOND L. LIBBY and AUSTIN L. JOYNER, J. Infect. Dis. **67**: 67 (July-Aug.) 1940.

"It has been shown that sulfathiazole [2-(paraaminobenzenesulfonamido)-thiazole] has considerably more in vitro activity than sulfapyridine [2-(paraaminobenzenesulfonamido)-pyridine] or sulfanilamide against the colon-typhoid-dysenteriae group of organisms. It is suggested that this drug be given clinical trials in this group of infectious diseases."

TOOMEY, Cleveland.

THE EFFECT OF AZOCHLORAMID ON CERTAIN PHYSIOLOGICALLY ACTIVE PRODUCTS OF STAPHYLOCOCCI. MARGARET D. HEISE and WILLIAM A. STARIN, J. Infect. Dis. **67**:70 (July-Aug.) 1940.

"Incubation of staphylococcus filtrates with azochloramid [N,N'-dichloroazodicarbonamidine] at 37 C. greatly reduced their hemolytic and dermo-necrotizing activities. The action on hemolysin appeared nearly complete after 6-8 hours. The plasma-coagulating factor was likewise inactivated, but the reaction apparently proceeded more slowly. Azochloramid added to cultures in amounts too small to inhibit growth was not observed to have any effect on the plasma-coagulating substance.

"The concentrations of staphylococcus toxin used in these experiments were considerably greater than those which might be expected in vivo. Nevertheless, the possibility that bacterial toxins may play an important part in wound infections gives practical significance to the results presented." TOOMEY, Cleveland.

ABRUPT INCREASE IN RESISTANCE TO CROTALUS VENOM. PRESTON KYES, LEO MARKIN and O. J. GRAHAM, J. Infect. Dis. **67**:81 (Sept.-Oct.) 1940.

"The conclusion to which we give emphasis is, that shortly following the intravenous injections of a sublethal dose of crotalus venom into pigeons there ensues a brief period during which the animals possess an increased tolerance for that venom." TOOMEY, Cleveland.

SURVIVAL OF PNEUMOCOCCI IN EMPYEMIC FLUID: EFFECT OF SULFAPYRIDINE UPON THEIR VIABILITY. ERWIN NETER, J. Infect. Dis. **67**:84 (Sept.-Oct.) 1940.

"The survival time of pneumococci in 12 specimens of human empyemic fluid, incubated in vitro at 37 C., ranged from 2 to 20 days with an average of 8 days." TOOMEY, Cleveland.

THE FAILURE OF SHOCKING AGENTS TO INFLUENCE THE MODE OF SPREAD OF VARIOUS VIRUSES IN THE CENTRAL NERVOUS SYSTEM. MARGARET HOLDEN, J. Infect. Dis. **67**:88 (Sept.-Oct.) 1940.

"The administration of shocking doses of either insulin or metrazol before intracerebral or intraperitoneal infection with "B" virus, herpes virus and St. Louis encephalitis virus failed to influence the course or the development of the respective diseases in adult mice. Metrazol given shortly after intraperitoneal infection with herpes or St. Louis encephalitis virus was similarly ineffective in facilitating the passage of the two viruses from the periphery to the central nervous system. The biochemical factors which are concerned with the spread of the three viruses from neural or extraneural sites of infection are evidently independent of the structural and functional changes induced by the shocking agents used in these experiments." TOOMEY, Cleveland.

THE RESPONSE OF DIFFERENT TYPES AND STRAINS OF PNEUMOCOCCUS TO SULFAPYRIDINE. L. H. SCHMIDT, CAROLYN HILLES, H. A. DETTWILER and EFFIE STARKS, J. Infect. Dis. **67**:232 (Nov.-Dec.) 1940.

"Sulfapyridine [2-paraaminobenesulfonamido)-pyridine] was uniformly more effective against experimental infections with type I pneumococcus than against infections with type III. Infections with certain type II strains responded as did type I pneumococcus, whereas infections with other strains responded as did type III.

"In vitro experiments showed that these type and strain variations were not related to differences in the bacteriostatic action of sulfapyridine. Nor were they due to retention of occasional organisms in isolated organs.

"It has been suggested that these differences in type and strain response were related to differences in antigenicity—the effectiveness of therapy being directly proportional to the capacity of the organisms to stimulate antibody formation." TOOMEY, Cleveland.

THE GERMICIDAL ACTION OF CLEANING AGENTS—A STUDY OF A MODIFICATION OF PRICE'S PROCEDURE. W. D. POHLE and L. S. STUART, J. Infect. Dis. **67**:275 (Nov.-Dec.) 1940.

These authors tested soaps and their germicidal activity by determining the rate of removal of transient and resident flora from the hands of 32 subjects by

washing. Ten basins were placed in a row, 2 liters of distilled water added to each and a certain amount of granulated soap put in every basin. The hands were then lathered for twenty or thirty seconds and the soap worked over the hands for seventy-five seconds; fifteen or twenty seconds was used in rinsing, the whole process taking two minutes. The process was repeated in each of the nine remaining basins, the hands not being dried during the interval. The total washing time was thus twenty minutes. They then drew up removal curves by plotting the bacterial counts per basin from the first to the tenth. It was concluded that an infinite number of washings would be necessary to get rid of all bacteria and bring the curve to zero.

With standards established by such a procedure, the authors believe that they could compare the results obtained with other soaps and even with treatment with regard to the removal of resident flora from the hands.

All sorts of organisms were found on the hands, some of which were peculiar to the individual subject. Usually the flora for a single subject was so characteristic that it attracted the attention of the observer and was a subject of frequent discussion. The authors' purpose was to obtain a method by which to evaluate the germicidal action of rosin soaps, but a practical result of this work was establishing the fact that in spite of the amount of washing done the resident flora of the hands still remained. It would take an infinite number of washings to make the hands even approach sterility. However, it is common clinical practice to rinse the hands in running water, and employing this procedure would materially affect results, though it must be mentioned that arriving at practical applications was not the purpose of this research. TOOMEY, Cleveland.

Metabolism; Infant Feeding; Milk and Other Foods

THE MANAGEMENT OF LACTATION AND OF DISORDERS OF THE BREAST IN THE PUERPERIUM. MEAVE KENNY, Practitioner **146**:18 (Jan.) 1941.

Every reader will account for the phenomenon of the decline in breast feeding in his own way. It is obvious, however, that the staffs of lying-in hospitals do their part to combat the decline, since nearly 90 per cent of women are breast feeding their babies when they leave the hospital at the end of the lying-in period. But after three months only about 55 per cent and after six months only 35 per cent are still nursing their infants. There seem to be factors working for the encouragement of the full exercise of the maternal function in the hospital that are lacking once the mother returns to her natural environment. It cannot be doubted that the greatest of these factors is suitable nourishment, a diet which is rich in fats, mineral salts and adequate fluid, and which is supplied in the hospital, especially in the form of milk. When the mother goes home the intake of milk, that begetter of milk, and other protective foods falls off, and the appeal of advertisements of baby foods becomes increasingly insistent as the production of breast milk wanes. This is the more likely if lactation has been deficient from the start. The importance of a good beginning is very great.

A discussion of the routine management of lactation, hormone therapy and the causes and treatment of mastitis is included. GELSTON, San Francisco.

ALIMENTARY EDEMA IN AN INFANT WITH ECZEMA. A. VAN WESTRIENEN, Maandschr. v. kindergeneesk. **10**:76 (Nov.) 1940.

The case of a breast-fed baby of 9 months who had eczema and alimentary edema is described. The child got such a small quantity of mother's milk that the ingestion of protein was very deficient, and the complementary feeding consisted only of carbohydrate and water. With the feeding of protein milk supplemented by vitamins the edema rapidly disappeared. The author warns against the use of a diet deficient in protein for children with eczema.

VAN CREVELD, Amsterdam, Netherlands.

Vitamins; Avitaminoses

KERATOMALACIA AND CYSTIC FIBROSIS OF THE PANCREAS. R. C. GAMBLE, Am. J. Ophth. **23**:539 (May) 1940.

Gamble gives a brief and interesting review of vitamin A deficiency and its symptomatology and pathology. He reports the case of a 3 month old boy who had keratomalacia in one eye. This improved apparently as the result of local use of percomorph liver oil. The response to general treatment was unsatisfactory, and the baby died. Autopsy revealed marked fibrosis of the entire pancreas. This evidently prevented assimilation of vitamin A, thus causing the keratomalacia and other symptoms.

W. S. REESE. [ARCH. OPHTH.]

THE PRESENT STATUS OF VITAMIN THERAPY. FREDERICK F. TISDALL, Am. J. Orthodontics **26**:1178 (Dec.) 1940.

Of the fifteen vitamins that have been demonstrated from animal experimentation, nine are necessary for human nutrition. They are A, four members of the B complex, C, D. E and K. A brief description of each vitamin is given, and from what source it may be obtained.

LEWIS, Dayton. [ANGLE ORTHODONTIST]

PREVENTION OF RICKETS IN PREMATURE INFANTS WITH PARENTERAL ADMINISTRATION OF SINGLE MASSIVE DOSES OF VITAMIN D. CARL ZELSON, J. Pediat. **17**:73 (July) 1940.

"Parenteral and oral vitamin D shock prophylaxis was carried out in forty-six premature infants. Only seventeen of them could be followed up to an age of from 44 to 279 days. During these periods, no rickets appeared in the premature infants who received 600,000 units of vitamin D_3 [calciferol] or D_3 [activated 7-dehydrocholesterol] parenterally.

"One premature infant who received 500,000 units of an oral vitamin D preparation on the twenty-first day of life showed rickets at the beginning of the fourth month. A second oral dose of 600,000 units of vitamin D_2 cured and prevented rickets up to the two hundred and sixty-second day of life."

RAUH, Cincinnati.

RIBOFLAVIN DEFICIENCY: REPORT OF A CASE IN A CHILD WITH CURE BY SPECIFIC TREATMENT. WILLIAM P. SHIELDS, New England J. Med. **223**:215 (Aug. 8) 1941.

Riboflavin deficiency is often evidenced by cheilosis. In such cases there are often manifestations of other deficiency diseases, such as pellagra, scurvy and polyneuritis.

A 6 year old girl of Italian descent had been born prematurely and had had no cod liver oil or orange juice since birth. The diet of the family was restricted because of a limited income, $6 a week being expended for food for a family of 6. The patient was the only member of the family in whom specific lesions developed. The lesions were ulcerating and involved the upper and lower lips, and there were deep transverse fissures at the angles of the mouth, not including the buccal mucosa.

Riboflavin was given in doses of 15 mg. daily for three days. Two days from the beginning of its administration there was almost complete resolution, and 10 mg. was then given for three days. But three days after the discontinuance of the drug, the lips showed signs of a relapse. Administration of the riboflavin was then continued till recovery ensued.

GENGENBACH, Denver.

SIGNIFICANCE OF VITAMIN B_1 (THIAMINE) FOR INFANTS. W. B. J. GERRITS, Maandschr. v. kindergeneesk. **10**:31 (Oct.) 1940.

After referring to the frequent occurrence of avitaminosis B_1 in infants (the beriberi of infants), especially in those countries where rice is the principal food, the author draws attention to hypovitaminosis B_1 in infants and older children. According to recent conceptions the latter type occurs in Europe and America. For the diagnosis of this hypovitaminosis the clinical symptoms, which are not specific, are not sufficient; it is necessary to demonstrate the deficiency by chemical analysis. Improvement of the symptoms after administration of vitamin B_1 adds support to the diagnosis.

The author studied the problem of the hypovitaminosis B_1 in infants and older children in the pediatric clinic at Amsterdam, Netherlands, by measurement of the excretion of thiamine in the urine by the thiochrome reaction of Jansen. It appeared that healthy infants (from birth to 2½ months of age) never excreted thiamine in the urine, regardless of their diet. The explanation of this phenomenon must probably be sought in the moderate supply of thiamine given to infants. The arguments for this conception are discussed.

The vitamin B_1 content of the main constituent of the infants' diet, that is, milk, proved to be low. The freezing of mother's milk only slightly decreased its vitamin B_1 content.

Infants 4 months of age and older did excrete thiamine in the urine, regardless of the diet. Infants between the ages of 2½ and 4 months excreted thiamine in the urine only if the main constituent of the diet was buttermilk. A probable explanation of this fact was discussed.

The significance of the determination of the thiamine excretion in the urine in pathologic conditions of infancy and childhood is stressed and illustrated by examples.

From his investigations the author draws some practical conclusions, namely, that additional thiamine should be administered to the infant soon after birth and a larger amount of the vitamin should be added to the mother's diet during pregnancy and lactation.

VAN CREVELD, Amsterdam, Netherlands.

ADMINISTRATION OF VITAMIN B_1 (ANEURIN) AS A THERAPEUTIC MEASURE. J. GOUDSMIT, Nederl. tijdschr. v. geneesk. **84**:25 (Jan. 6) 1940.

After a brief discussion of the symptoms caused by lack of vitamin B_1, the possibilities are mentioned by which a shortage of the vitamin may arise. The exact methods for the recognition of vitamin B_1 deficiency are mentioned. The indications for treatment with the vitamin are given and the technic of treatment described.

VAN CREVELD, Amsterdam, Netherlands.

Newborn

PROBABLE ACTION OF VARIOUS ESTROGENS ON THE PHYSIOLOGIC LOSS OF WEIGHT IN THE NEWBORN. A. MICHELONI, Med. ital. **21**:125 (March) 1940.

There is a physiologic loss of weight in the newborn infant soon after birth. The author found that by giving large doses of various preparations of estrogen this loss of weight could be prevented in the majority of 70 newborn infants. The author offers no explanation for their action.

MARTOCCIO, Utica, N. Y.

UMBILICAL SEPSIS IN THE NEWBORN. A. VAN WESTRIENEN, Maandschr. v. kindergeneesk. **9**:492 (Sept.) 1940.

A case of umbilical sepsis in an infant of 10 days with a perfectly sound umbilicus is described. The diagnosis was based on the swelling of the abdominal wall between the umbilicus and the symphysis pubis. The infant died, and the

diagnosis was confirmed at necropsy. There were cellulitis of the subcutaneous tissue and hyperemia of the peritoneum. The lymphangitis in the subcutaneous tissue was accompanied by arteritis. VAN CREVELD, Amsterdam, Netherlands.

Acute Contagious Diseases

OCULAR COMPLICATIONS OF MENINGOCOCCIC MENINGITIS. P. M. LEWIS, Am. J. Ophth. **23**:617 (June) 1940.

Lewis gives the following summary of his study:

"The eyes of 350 patients with meningococcic meningitis have been examined over a period of nine years. Repeated examinations were made when indicated. The findings of numerous other observers are given as well as those of the author. Each structure of the eye is considered separately and its complications described. Any of the structures of the eye may be involved, and very occasionally all are affected. In this series of 350 cases, 44 per cent showed some deviation from the normal. Deducting 14 per cent, which showed only an engorgement of the retinal veins, there remain 30 per cent with definite pathologic changes. The most frequent complication in this series was papillitis. Papilledema was quite rare.

"Metastatic endophthalmitis was the most spectacular and also the most disastrous complication. Photomicrographs of several eyes enucleated for endophthalmitis, with a brief description of the pathologic findings, have been included.

"The modern treatment of meningococcic meningitis by antitoxin and sulfanilamide is recommended, but not described in detail. Frequent ocular examination of all cases is urged."

W. S. REESE. [ARCH. OPHTH.]

IMMUNITY IN MONKEYS RECOVERED FROM PARALYTIC ATTACKS OF POLIOMYELITIS. JOHN F. KESSEL and FRED D. STIMPERT, J. Immunol. **40**:61 (Jan.) 1941.

The authors state that previous workers have reported widely varying results in studies of immunity in monkeys following attacks of poliomyelitis. Of 149 inoculated animals, 61 per cent exhibited complete immunity and 30 per cent partial immunity. Recovered monkeys were more often immune to homologous than to heterologous strains of virus. The authors emphasize that the amounts of virus used for these second inoculations were large; hence, the results of these experiments need not discourage workers attempting to develop antigens for the production of practical clinical immunity.

BILLINGTON, Seattle.

HYPERTENSION IN DIPHTHERIA. IRVING ROSENBAUM JR., J. Pediat. **17**:210 (Aug.) 1940.

"Two cases of postdiphtheritic paralysis accompanied by hypertension are reported. The blood pressure increased as the paralysis progressed and gradually decreased as the paralysis cleared. Several comparable cases were cited from the literature. Review of the literature reveals that the occurrence of hypertension in children is not uncommon.

"Various etiological possibilities were mentioned. It seems most likely that late hypertension coming on at the time of paralysis is of neurologic origin, attributed either to damage to a center in the medulla or mediated by irritation of nerve fibers similar to the carotid sinus reflex."

RAUH, Cincinnati.

OBSTETRIC EXPERIENCES OF WOMEN PARALYZED BY ACUTE ANTERIOR POLIOMYELITIS. S. KLEINBERG and T. HORWITZ, Surg., Gynec. & Obst. **72**:58 (Jan.) 1941.

Kleinberg and Horwitz determined the effect of acute anterior poliomyelitis on 243 women who had subsequent pregnancies. They examined 44 of the women,

and the data on the remaining 199 were obtained through questionnaires filled out by the attending obstetrician and orthopedic surgeon and in some instances by the patient. In the series there were 13 women whose pregnancy was complicated by an acute attack of anterior poliomyelitis. Asymmetry of the pelvic inlet was found among approximately 80 per cent of the women. The distortion was usually mild and did not produce dystocia. Pelvic asymmetry was absent in those who because of extensive paralysis were completely bedridden, never having attempted to bear weight or to get about with braces and crutches. There were four main types of pelvic deformity: lateral pelvic obliquity; increased anterior pelvic tilt with exaggerated lumbar lordosis; anteroposterior axis deviation or rotation about a longitudinal axis, and rotation of one innominate bone on the other about a transverse axis or torsional deformity. From 15 cases reported in the literature, 1 case reported to them and the 13 cases collected by them the authors conclude that pregnancy complicated by acute anterior poliomyelitis may be anticipated to progress normally, with a normal termination of labor and with normal offspring. The involuntary contractions of the uterus and the ability of the uterus to expel its contents spontaneously, also observed in patients paralyzed by tumor of the cord, spondylitis or vertebral fracture, are due to the fact that the uterus has an independent nerve supply and will contract after the spinal cord is transected and after its sympathetic nerve supply is extirpated. There was no instance of intrauterine poliomyelitis among the 29 cases. The passive immunity of the offspring derived from the mother does not persist for long, as a few cases of acute anterior poliomyelitis in infants less than 1 month of age (earliest, 9 days) have been reported. Analysis of the 243 cases in which the patient became pregnant one year or more after an acute attack of anterior poliomyelitis reveals that a normal and uneventful pregnancy and labor with normal offspring may be anticipated. There is no indication for interruption of pregnancy, except those reasons that would also be operative in cases of nonparalytic women. Cesarean section was utilized in a higher percentage (11.5) of the paralytic women than in a comparable nonparalytic series, but it is the authors' belief that in some instances it may not have been warranted and that therefore the percentage probably does not represent the true index of the need of cesarean section for paralytic women.

J. A. M. A.

MEASLES AND PNEUMONIA COMPLICATED BY THE TOXIC EFFECTS OF SULPHAPYRIDINE. M. C. PUCKEY, M. J. Australia **1**:52 (Jan. 11) 1941.

A case of measles and bronchopneumonia complicated by hepatitis during sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) therapy is reported. The patient responded well to treatment with calcium gluconate.

GONCE, Madison, Wis.

PARALYSES OCCURRING IN THE COURSE OF MENINGOCOCCIC MENINGITIS. P. FORT and M. IGERT, Presse méd. **48**:693 (Sept. 4-7) 1940.

Six cases are reported in which paralysis of the lower extremities occurred during the treatment of meningococcic meningitis. In all but 1 case sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) had been given intrathecally. One leg was involved severely and the other lightly. Sensation was impaired. Sphincter control was lost. The patient who received no intrathecal chemotherapy had monoplegia, with no loss of sphincter control.

DAFFINEE, Boston.

EPIDEMIOLOGY AND PROPHYLAXIS OF ACUTE POLIOMYELITIS. R. CLEMENT, Presse méd. **48**:766 (Sept. 25-28) 1940.

This is a review of the present knowledge of the transmission and prevention of this disease.

DAFFINEE, Boston.

SUBACUTE INFANTILE POLIOENCEPHALITIS ANTERIOR. A. GAREISO and J. P. KÄFER, Rev. neurol. de Buenos Aires **6**:1 (Jan.-March) 1941.

In a boy of 13, who had previously been healthy, there gradually developed bulbar palsies affecting the lips, tongue and larynx without involvement of sensation, the pyramidal tract, the cerebellum or the cerebral cortex. The blood and spinal fluid were normal. He died of bronchopneumonia seven months from the onset.

Autopsy revealed atrophy of the cells of the bulbar medullary nuclei and degeneration of the peripheral portions of the nerves springing from them, with minimal glial proliferation and no degeneration of the white matter.

Cases of such a condition are rare, but their existence should be recognized.

J. A. M. A.

POLIOMYELITIS ANTERIOR ACUTA IN A CHILDREN'S HOME. A. VISSER, Nederl. tijdschr. v. geneesk. **84**:395 (Feb. 3) 1940.

Examination of all the inmates of a children's home in which 2 cases of acute anterior poliomyelitis had occurred showed that all of the children and the majority of the nursing staff showed abnormalities of the cerebrospinal fluid of the same kind as are present in this disease. Thus children, as well as adults, living near a patient with poliomyelitis may be infected by the virus although they show only slight symptoms of the disease.

VAN CREVELD, Amsterdam, Netherlands.

Chronic Infectious Diseases

INCREASED RESISTANCE TO SYPHILIS IN THE RABBIT FOLLOWING PROLONGED ADMINISTRATION OF URINARY ESTROGENS. CHESTER N. FRAZIER and CH'UAN-K'UEI HU, Endocrinology **28**:294 (Feb.) 1941.

Male rabbits which had been feminized by prolonged treatment with estrogenic substance showed a much greater resistance to syphilitic infection than normal males. The mechanism through which resistance was enhanced was not revealed.

JACOBSEN, Buffalo.

EVALUATION OF MANTOUX TUBERCULIN TEST WITH HUMAN AND BOVINE TUBERCULIN FOR DIAGNOSIS OF OCULAR DISEASES, WITH SPECIAL CONSIDERATION OF THRESHOLD REACTION. H. SCHLICHTING, Klin. Monatsbl. f. Augenh. **104**:401 (April) 1940.

In discussing the value of the diagnostic tuberculin test, Schlichting points out some errors and uncertainties connected with it. With two exceptions the subject is free from tuberculosis if the test shows no evidence even with a large dose. The reaction will not show positive results until several weeks after a tuberculous infection. Sensitivity to tuberculin may be greatly reduced or even eliminated in patients with advanced tuberculosis in the presence of measles, croupous pneumonia, scarlatina, epidemic meningitis, grip, typhoid fever, pertussis or varicella and after therapeutic injections of tuberculin. A positive reaction to tuberculin is proof that the subject is infected with tuberculosis but not that he is sick. Schlichting discusses the value of the intracutaneous test with tuberculin and adds a number of tables. Intracutaneous injections of human or bovine tuberculin were given to 87 persons suspected of having ocular tuberculosis and to 87 healthy controls. The weakest solution of tuberculin which elicits a reaction was used. No essential difference in action was found between human and bovine tuberculin. The reaction in persons suspected of having tuberculosis and that in healthy persons showed no important difference. As a rule the actually tuberculous patient showed a negative reaction or a positive reaction only to a

high concentration. The intracutaneous reaction to tuberculin therefore appears to be unreliable as a test of the possible tuberculous nature of an ocular disease.

K. L. STOLL. [ARCH. OPHTH.]

Diseases of Blood, Heart and Blood Vessels and Spleen

USE OF SERIAL DILUTIONS IN DETERMINATION OF PROTHROMBIN BY THE ONE STAGE TECHNIC. J. GARROTT ALLEN, ORMAND C. JULIAN and LESTER R. DRAGSTEDT, Arch. Surg. **41**:873 (Oct.) 1940.

"Experimental data are presented here concerning the determination of prothrombin by a modified one stage technic. All determinations were carried out at 37 C., with lung extract as the thromboplastic substance and with a test of normal human plasma run with each group of determinations. Clotting times were determined on ten serial dilutions of each plasma, with concentrations ranging from 50 per cent to 5 per cent of the original undiluted plasma. A final standard volume was maintained with oxalated saline solution in each sample. All volumetric measurements were made with micropipets."

The advantages of this method are discussed.

KAISER, Rochester, N. Y.

REDUCTION OF ARTERIAL BLOOD PRESSURE OF HYPERTENSIVE PATIENTS AND ANIMALS WITH EXTRACTS OF KIDNEYS. IRVINE H. PAGE, O. M. HELMER, K. G. KOHLSTAEDT, P. J. FOUTS and G. G. KEMPF, J. Exper. Med. **73**:7 (Jan.) 1941.

Methods of preparing the kidney extract are given. The extracts are most effective when administered parenterally, but they may be given by mouth or by rectum. The authors report that hypertensive patients were both objectively and subjectively improved after administration of the kidney extract. Blood pressure in some patients and in some animals remained lowered for a period ranging from several days to several weeks after administration of the extract was discontinued.

BILLINGTON, Seattle.

A STANDARDIZATION TECHNIQUE FOR SEDIMENTATION RATE. J. W. CUTLER, J. Lab. & Clin. Med. **26**:542 (Dec.) 1940.

A simple method for the determination of the erythrocyte sedimentation rate is described. The test can be done in thirty minutes, and no correction for anemia is necessary.

CARD, Galveston, Texas.

A CLINICAL STUDY OF THE WELTMANN SERUM COAGULATION REACTION. SUSAN COONS DEES, J. Pediat. **17**:44 (July) 1940.

The technic of performing the Weltmann serum coagulation test is outlined. A compilation of the results of the clinical application of this test to a variety of diseases reported in the literature is given. The results of the Weltmann test performed on 246 patients in the pediatric service of the University of Minnesota Hospital are reported. The value of this simple laboratory test in evaluating acute inflammatory and chronic fibrotic processes and its usefulness in detecting hepatic damage in a variety of conditions are stressed.

RAUH, Cincinnati.

AN EXPERIMENTAL STUDY OF THE WELTMANN SERUM COAGULATION REACTION. SUSAN COONS DEES, J. Pediat. **17**:53 (July) 1940.

The fundamental physicochemical or physiologic mechanism underlying the Weltmann reaction is still obscure. The experimental studies on which this report is based were undertaken to determine whether the reaction could be modified or influenced by artificial means, either in vivo or in vitro. Dees found that the coagulum is protein in nature and that an amount of protein greater than 0.2 mg.

per hundred cubic centimeters of fluid is necessary for the production of the flocculum. The p_H of serum or of a serum–calcium chloride mixture has no effect on or relation to the reaction. The injection of foreign serum has no uniform effect on the coagulation band. Calcium is essential for the coagulation reaction. Coagulation did not occur when calcium was removed from the system, and calcium injected intravenously tended to prolong the coagulation band for a short time. The colloid acacia injected intravenously prolonged the coagulation band slightly for four hours. Sodium ricinoleate produced a shortening of the band, in vitro and in vivo. Oleic and palmitic acids greatly lengthened the band in vitro. Olive oil produced a similar but less marked effect. In acute infectious states in which the level of fatty acids in the blood is low the coagulation band is short, and in anemia, leukemia, nephritis and diabetes, in which the band is long, there is an elevation of the level of fatty acids in the blood. It is suggested that serum lipids are a decisive factor in determining the length of the coagulation band.

RAUH, Cincinnati.

THE INVOLVEMENT OF THE NERVOUS SYSTEM IN SICKLE-CELL ANEMIA. JAMES G. HUGHES, L. W. DIGGS and CLARENCE E. GILLESPIE, J. Pediat. **17**:166 (Aug.) 1940.

"Central nervous system involvement is a frequent occurrence in sickle-cell anemia.

"Reports of six new cases, two with autopsy, are presented, and the available literature including twenty-five other cases is reviewed.

"The clinical manifestations and spinal fluid findings are summarized.

"The essential pathology in the brain in sickle-cell anemia is similar to the pathology in other organs. The lesions are multiple and widespread but are mainly localized in the peripheral cortex and meninges. We consider the lesions to be primarily intravascular and due to thrombosis, following which there are extension of the thrombotic process and hemorrhagic, degenerative, and atrophic changes.

"Prognosis is poor, but variable and unpredictable."

RAUH, Cincinnati.

CHRONIC LYMPHATIC LEUKEMIA. CHARLES BROOKINGS, Bol. Inst. de puericult. **2**:5, 1940.

In the case reported, that of a 1½ year old white infant, the clinical diagnosis was whooping cough. However, examination of the blood showed large lymphocytes, many small lymphocytes and several plasma cells. Consequently, the diagnosis of primary chronic lymphatic leukemia was proposed by the author, who goes on to discuss the classification and history of the leukemias. He comments on the relative advantages of obtaining material for biopsy by sternal and by splenic puncture. He considers the latter procedure disadvantageous for work with children. Treatment is fully discussed, but only roentgen therapy and the administration of thorium salts and arsenic are considered useful.

After making some general remarks on hematopoiesis, Dr. Brookings recommends that accurate differential blood counts be made for all patients with chronic adenopathy or eczema.

SOTO, Habana, Cuba.

CONGENITAL HEART BLOCK. E. GORTER, Maandschr. v. kindergeneesk. **10**:46 (Nov.) 1940.

A case of complete congenital atrioventricular dissociation in a baby 7 months old is described. In addition, the child had congenital heart failure, characterized by marked polycythemia, a diastolic murmur and hypertrophy of the heart. The report of a case of partial heart block, previously published, with an electrocardiogram is also given. In the majority (85 per cent) of the 80 reported cases congenital heart block was complete; very often there existed at the same time an open septum ventriculorum. In many cases the diagnosis was made before or soon after birth. Attacks of syncope occur in 20 per cent of the cases. Necropsy

always shows that the connection between Tawara's node and the bundle of His is interrupted; often the right branch of this bundle is lacking. The prognosis of heart block depends on the presence of other congenital cardiac anomalies and the occurrence of attacks of Stokes-Adams syncope.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of the Nose, Throat and Ear

DIARRHEA AND LATENT MASTOIDITIS. R. THIBAUDEAU, Union méd. du Canada **69**:588 (June) 1940.

The author presents the cases of 6 infants in which latent mastoiditis was responsible for chronic diarrhea. In 2 cases operation was refused and the baby died. Observations at autopsy in each case proved that no other focus of infection could be held responsible. The infants who underwent operation recovered.

DAFFINEE, Boston.

A NEW PLASTIC METHOD FOR CLOSURE OF RETROAURICULAR FISTULA AFTER RADICAL OPERATION ON THE MIDDLE EAR. D. G. W. VAN VOORTHUYSEN, Nederl. tijdschr. v. geneesk. **84**:5120 (Dec. 28) 1940.

A new method is described for plastic closure of a retroauricular fistula resulting from a radical mastoid operation, by means of a plastic pedicle flap of the normal skin above or below the fistula. By this method also dislocation of the concha may be corrected.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of Lungs, Pleura and Mediastinum

THE ROLE OF BRONCHOSCOPY IN THE TREATMENT OF PULMONARY ABSCESS. CHEVALIER L. JACKSON and A. R. JUDD, J. Thoracic Surg. **10**:179 (Dec.) 1940.

The authors review 124 cases of nontuberculous pulmonary abscess in which it was proved by roentgen examination that unilocular cavities were present. In 113 a bacteriologic study of bronchoscopically removed bronchial secretions was carried out. There were twice as many male as female patients. The most common cause was a preceding surgical operation. Among the surgical procedures, tonsillectomy predominated; general anesthesia was employed in all stated instances except 3. The right lung was affected in 91 cases.

Mortality figures remain high. There was a 29.4 per cent mortality rate in 78 cases in which conservative treatment was used. The surgical mortality in 37 cases was somewhat higher, but these included a few cases in which treatment with procedures now generally abandoned was employed. External drainage proved to be the most effective surgical measure and is recommended in all cases in which surgical intervention is required, except when complicating conditions demand lobectomy or pneumonectomy. Surgical intervention is recommended when progress is not rapid and unmistakable.

Otherwise conservative treatment is advised. This includes such measures as rest in bed, good nursing care, dietary and symptomatic treatment, postural drainage, bronchoscopic examination, transfusions, vaccines, intravenous therapy and administration of neoarsphenamine.

DORSEY, Chicago.

CYSTS OF THE LUNG IN CHILDHOOD: REPORTS OF TWO CASES. J. C. SCHIPPERS, Maandschr. v. kindergeneesk. **10**:17 (Oct.) 1940.

Two cases in which there was great difficulty in making the diagnosis are described. In 1 case there were several communicating cysts containing fluid in one lung; in the other there were large air-filled cysts in one lung, which resulted in a picture resembling pneumothorax.

VAN CREVELD, Amsterdam, Netherlands.

PULMONARY COLLAPSE IN CHILDREN. E. J. MEYERS, Maandschr. v. kindergeneesk. **10**:41 (Nov.) 1940.

A short survey is given of the causes, roentgenologic picture, clinical symptoms, complications and treatment of pulmonary collapse in children. In Netherlands the symptoms and complications of this condition were especially stressed by the late Dr. M. de Bruin, from whose publications and notes this article has been composed.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

THE TREATMENT OF ACUTE STOMATITIS. CHARLES HENDEE SMITH and HERBERT B. JOHNSON, J. Pediat. **17**:1 (July) 1940.

This paper discusses the treatment of acute gingivostomatitis. So many remedies have been recommended that it is probable that most of them are worthless. The authors present a technic for treatment which has been highly satisfactory. The mouth is cleansed with a weak solution of hydrogen peroxide to remove accumulated sordes or sloughing material, and this is followed by a mouth wash, compound solution of sodium borate (Dobell's solution) or a solution of sodium perborate being used. The gums and ulcers are then dried carefully with several swabs of cotton. Then a 5 to 7 per cent solution of chromic acid is applied by cotton swab directly to the ulcers and the inflamed gums. This treatment is repeated twice daily for one to three days and then once daily. Between treatments the patient may use a mouth wash. Supportive treatment such as is used for any febrile illness must be given. The chromic acid has a definite analgesic effect, and the patients are able to eat with more comfort for several hours after treatment. There is rapid improvement in the inflamed gums, and the course of the disease is definitely shortened, especially in those cases in which treatment is begun early.

RAUH, Cincinnati.

DISTURBANCE OF OSSEOUS AND LIPID METABOLISM IN A CHILD WITH PRIMARY CARCINOMA OF THE LIVER. ARILD E. HANSEN, MILDRED R. ZIEGLER and IRVINE MCQUARRIE, J. Pediat. **17**:9 (July) 1940.

This is a report of an unusual case of primary carcinoma of the liver in a 10 year old boy. The tumor was of slow growth. The first symptoms occurred approximately two years before death. The tumor was of the destructive type; it caused impairment of certain hepatic functions without causing measureable jaundice until near the end of life. The most striking clinical features were marked hyperlipemia with extensive lipid histiocytosis of various organs and extreme osteoporosis. Chemical and histologic examination of the bones showed that the osteoporosis was not due to lipid infiltration. The results of a mineral balance study indicated that it was due to defective retention of calcium and phosphorus by the osseous system. Since this defect in retention manifested itself despite an adequate intake of vitamin D and without evidence of hyperparathyroidism or impairment of the absorption of calcium and phosphorus from the gastrointestinal tract, it was tentatively concluded that the liver normally plays an essential role in osseous metabolism. It appears that this function was seriously impaired in this case.

RAUH, Cincinnati.

THE GLUCOSE TOLERANCE TEST IN CELIAC DISEASE: SIGNIFICANCE OF LOW BLOOD SUGAR CURVES. CHARLES D. MAY and JOHN F. MCCREARY, J. Pediat. **17**:143 (Aug.) 1940.

A low blood sugar curve is obtained in the dextrose tolerance test in cases of celiac disease, sprue, cretinism, disease of the pancreas and infection and in the presence of malnutrition alone. It has been established that in celiac disease the

low blood sugar curve is due to delayed or defective absorption of carbohydrate from the intestine, but the mechanism by which this delayed or diminished absorption takes place has not been established. The authors, by means of a series of studies on normal infants and children and others suffering from celiac disease and allied diseases, point out the importance of motility of the gastrointestinal tract and impairment of absorption from the intestine in the causation of a low blood sugar curve. These studies include an oral dextrose tolerance test, which was performed to determine the nature of the blood sugar curve. Then the influence of the emptying mechanism of the stomach was eliminated by introducing the dextrose directly into the duodenum through a tube. In some cases mecholyl-chloride (acetylbetamethylcholine hydrochloride) was administered simultaneously into the duodenum to maintain vigorous activity of the small intestine. In some instances a barium sulfate meal was given at the time of these tests; the motility of the gastrointestinal tract was observed under a fluoroscope. The results of these experiments bring support to the hypothesis that the blood sugar curve in the dextrose tolerance test is affected by the motility of the gastrointestinal tract, including the emptying of the stomach and the peristalsis and segmentation in the small intestine. In celiac disease and allied conditions there is no specific defect in absorption of carbohydrate by the intestinal mucosa, but the low blood sugar curve seems to be due to the inactivity of the gastrointestinal tract, with consequent inefficient absorption.

RAUH, Cincinnati.

PRIMARY CARCINOMA OF THE LIVER, WITH BANTI'S SYNDROME. VIDA B. WENTZ and KATSUJI KATO, J. Pediat. **17**:155 (Aug.) 1940.

A case of primary carcinoma of the liver in a 6 year old girl is reported. Pronounced cirrhotic changes in the liver, which resulted in the development of a collateral circulation (caput medusae), esophageal and gastric varices (hematemesis), splenomegaly, ascites and a hypoplastic blood picture were present. The symptom complex bearing the name of Banti, which is characerized by splenomegaly associated with cirrhosis of the liver, jaundice, ascites and a hypoplastic blood picture, is discussed. Three distinct types of disease included in this symptom complex are described, namely, Banti's disease proper, the Smith-Howard-Wallgren syndrome and neoplastic disease of the liver.

RAUH, Cincinnati.

HYPOVITAMINOSIS OF ALL FAT-SOLUBLE VITAMINS DUE TO STEATORRHEA. FULLER ALBRIGHT and JOHN D. STEWART, New England J. Med. **223**:239 (Aug. 15) 1940.

It is well recognized that steatorrhea may be associated with hypocalcemia and tetany. It is the object of this paper to report a case of fatty diarrhea in which there was insufficiency of at least three of the fat-soluble vitamins and to emphasize the importance of administering all the fat-soluble vitamins in such cases, rather than vitamin D alone.

The patient had had uncontrolled tetany for the past month; numerous subcutaneous hemorrhages began to occur over the entire body, and the red blood cell count fell rapidly. Shortly after admission to the hospital an eruption developed on the breast and abdomen, which was diagnosed as xeroderma.

Daily administration of 500,000 U. S. P. units of vitamin D was begun. The tetany responded readily to this treatment, and the level of calcium in the serum rose from 7 to 10 mg. per hundred cubic centimeters during a period of three weeks. The level of phosphorus in the serum also rose from 4.1 to 5.1 mg. and the level of protein from 4.6 to 6.4 Gm. per hundred cubic centimeters.

The vitamin K deficiency (clotting time, over ninety minutes) was treated by the oral administration of 1 mg. of 2-methyl-1, 4-naphthoquinone in corn oil and 9 grains (0.58 Gm.) of desoxycholic acid daily. The concentration of prothrombin

in the plasma rose rapidly, and within twenty-four hours it was 60 per cent of normal and the bleeding tendency was under control.

Vitamin A was given in the form of Lederle's vi-delta liquid concentrate. The patient received 45 drops of this preparation (about 89,100 U. S. units of vitamin A) daily. The vitamin A content of the serum rose from 8.2 per hundred cubic centimeters (normal, 10 to 20 units), and the carotenoids during the same time rose from 0.77 to 6.5 units (normal 30 to 80 units). There was a definite improvement in the xeroderma during this period. The weight increased from 85 to 123 pounds (38.6 to 55.8 Kg.).

GENGENBACH, Denver.

CONGENITAL OBSTRUCTION OF DUODENUM. EUGENE B. POTTER, Northwest Med. **39**:261 (July) 1940.

A case of congenital obstruction of the duodenum in a child 6 years of age and weighing 25 pounds (11.3 Kg.) is reported. The obstruction seemed to be due to compression of the duodenum by the superior mesenteric vessels and the mesentery of the small intestine. Treatment consisted of duodenojejunostomy. Within three weeks after the operation the patient gained 15 pounds (6.8 Kg.).

ROBERTSON, Omaha.

MECKEL'S DIVERTICULUM, WITH ECTOPIC GASTRIC TISSUE PERFORATION AND HEMORRHAGE. S. F. HERRMANN, C. P. LARSON and B. A. BROWN, Northwest Med. **39**:337 (Sept.) 1940.

A case is reported in which the diverticulum essentially represented an accessory stomach and produced complications of marginal ulcer, with hemorrhage and perforation. The patient, an 11 year old boy, complained of pain in the lower part of the abdomen, accompanied by nausea, diarrhea and constipation. During the preceding three years his condition had been diagnosed as acute appendicitis, which was not relieved by appendectomy, and pyelocystitis. After the development of a draining sinus a diagnosis of Meckel's diverticulum was made.

ROBERTSON, Omaha.

A REVIEW OF THE LITERATURE CONCERNING HAEMORRHAGE IN OBSTRUCTIVE JAUNDICE: THE SIGNIFICANCE OF PROTHROMBIN AND OF VITAMIN K. THERAPY. J. D. HICKS, M. J. Australia **1**:46 (Jan. 11) 1941.

Hicks reviews the vast literature on the subject indicated by the title.

GONCE, Madison, Wis.

JAUNDICE IN CHILDHOOD, WITH SPECIAL REFERENCE TO INFANCY. S. VAN CREVELD, Geneesk. gids **17**:40 (Jan. 17); 60 (Jan. 24) 1941.

The different forms of jaundice which occur in childhood, especially in infancy, are discussed in detail. The points discussed are illustrated by clinical observations from a large number of the author's cases. Stress is laid on the differential diagnosis. Among the diseases in older children in which jaundice may be an important symptom the following are mentioned especially: cirrhosis of the liver, Weil's disease, septic conditions, jaundice produced by administration of arsphenamine, congenital and acquired hemolytic jaundice, scarlet fever and glandular fever.

AUTHOR'S ABSTRACT.

TREATMENT OF CONGENITAL PYLORIC HYPERTROPHY. J. DRUKKER, Maandschr. v. kindergeneesk. **10**:105 (Dec.) 1940.

Six patients with congenital pyloric stenosis were treated with eumyldine (atropine methylnitrate). The results were disappointing; all but 1 had to be operated on. The Fredet-Weber-Rammstedt operation remains the treatment of

choice for the severe type of the condition. In accordance with the results of Faber and Davis (Gastric Peristalsis After Pylorostomy in Infants, *J. A. M. A.* **114**:847 [March 9] 1940), the author advises against oral feeding during the first twenty-four hours after operation; thereafter 30 Gm. of food is given every four hours, and on subsequent days the quantity of food is gradually increased.

VAN CREVELD, Amsterdam, Netherlands.

Nervous Diseases

EXPERIMENTAL AND CLINICAL STUDIES IN HYDROCEPHALUS. J. Q. GRIFFITH, W. E. FRY and A. MCGUINNESS, Am. J. Ophth. **23**:245 (March) 1940.

Previous work is referred to and briefly discussed and the following summary given:

"When thorotrast [colloidal thorium dioxide] is injected into the cisterna magna of the rat it spreads about the subarachnoid space and usually enters the ventricles. From the subarachnoid space it extends along the perineural pathways, especially those of the optic nerves, outlining them as seen in the roentgenograms. From the ventricle it is absorbed along the perivascular spaces of the vein of Galen and its tributaries, probably eventually reaching the spaces about the straight sinus, the lateral sinus, the internal jugular vein, and draining to the cervical lymph nodes. Thorotrast outlines the perivascular space of the vein of Galen more regularly after injection into the ventricle than after intracisternal injection. Hydrocollag injected into the ventricle may be identified histologically in the perivascular space of the vein of Galen.

"An intracisternal injection of kaolin tends to block the perineural optic space and, less regularly, the perivascular space of the vein of Galen. Thus a subsequent injection of thorotrast does not regularly outline these spaces. Blood from a subarachnoid hemorrhage has the same effect as kaolin, but acts less efficiently. Papilledema results if there is increased flow of fluid, or transmission of increased pressure, along a patent perineural optic space. This occurs in obstruction of the aqueduct; therefore, papilledema is associated with noncommunicating hydrocephalus. Communicating hydrocephalus is associated with, and is possibly caused by, block of both perineural absorption and of perivascular absorption from the ventricle. Therefore papilledema does not usually occur in communicating hydrocephalus. Analysis of clinical material showed that 45 out of 49 cases conformed to these conclusions drawn from the experimental data."

W. S. REESE. [ARCH. OPHTH.]

LOCALIZED NONSUPPURATIVE ENCEPHALITIS SECONDARY TO INFECTIONS OF THE TEMORAL BONE AND PARANASAL SINUSES, WITH A REPORT OF FOUR CASES. JOSEPH C. YASKIN, J. Nerv. & Ment. Dis. **92**:281 (Sept.) 1940.

Yaskin reports 4 cases in which signs of localized disease of the brain followed infection of the temporal bone or the paranasal sinuses. The signs included various paralyses, aphasias, anesthesias or cerebellar dysfunction, with or without evidences of increased intracranial pressure; moderate pleocytosis, and usually restlessness, irritability or delirium. In 3 of the cases mastoid infection was responsible, spreading in 2 cases to the temporal lobe and in 1 to the cerebellum. In the fourth case frontal, ethmoid and maxillary sinusitis was followed by evidence of focal disease of the right temporoparietal region. In this case the pressure of the cerebrospinal fluid was elevated and the cell count 150, with predominance of lymphocytes. All the patients recovered without development of abscess of the brain, after adequate treatment of the original infection. Yaskin states that the pathogenesis and morbid anatomy in such cases are not known and that the diagnosis is difficult, since the condition seems to represent only a stage in the development of an abscess which never materializes. He emphasizes the importance

of prompt eradication of the responsible focus of infection and the avoidance of too early exploration of the brain for possible abscess.

MACKAY, Chicago. [ARCH. NEUROL. & PSYCHIAT.]

THE TREATMENT OF MENINGITIS DUE TO HAEMOPHILUS INFLUENZAE (PFEIFFER'S BACILLUS): A REVIEW OF ONE HUNDRED AND EIGHT CASES. JANVIER W. LINDSAY, E. CLARENCE RICE and MAURICE A. SELINGER, J. Pediat. **17**:220 (Aug.) 1940.

"Meningitis due to H[aemophilus] influenzae is relatively common in children. Excluding tuberculous meningitis, it is the commonest cause of meningitis in children under 2 years of age. . . .

"The treatment of this type of meningitis with specific serum and human complement intrathecally, intravenous serum, with adequate supportive treatment consisting of transfusions, fluids and vitamins, has reduced the mortality percentage from 97 to 83. By adding sulfanilamide and sulfapyridine [2-(paraaminobenzene-sulfonamido)-pyridine] to the above, the mortality for thirteen cases has been further reduced to 54 per cent."

RAUH, Cincinnati.

EPILEPSY: OBSERVATIONS ON TREATMENT. FREDERICK LEMERE, Northwest Med. **39**:289 (Aug.) 1940.

About 1 person in 10 shows abnormal brain waves on electroencephalographic examination, and the obvious conclusion is that such a person has inherited a constitutional tendency to epilepsy. Clinical epilepsy actually develops in only 1 person in 20. It seems unwise for 2 persons with abnormal brain waves to have children.

In the treatment of epilepsy bromides and phenobarbital are being superseded by dilantin sodium. Medication should be continued for at least a year after the last seizure.

The modern outlook on epilepsy should be one of hope, as the majority of patients can be kept free of symptoms or greatly helped by proper treatment.

ROBERTSON, Omaha.

LEBER'S PRIMARY OPTIC ATROPHY WITH OTHER CENTRAL NERVOUS SYSTEM INVOLVEMENT. S. ANDROP, Psychiatric Quart. **15**:215 (April) 1941.

Androp reports 2 cases of Leber's disease in which neurologic evidence of other involvement of the nervous system was found. No report of the pathologic changes has as yet been made, leaving an important step in the evaluation of this disease unaccomplished.

The 2 cases reported were those of brothers in a family known to be heavily tainted with visual disorders for three generations. One of the patients had a schizophrenic psychosis. He showed slight tremor of the fingers and hyperactive reflexes in the lower extremities. The gait was broad based and clumsy. The second patient showed progressive speech disturbances, poor coordination, muscular underdevelopment and weakness of the flexor, adductor and abductor muscles of the fingers and toes. There were slight choreoathetoid movements of the tongue and mouth muscles. The deep reflexes were decreased in the upper extremities and hyperactive in the lower. Speech was stammering and slurring. These cases are considered instances of Leber's disease, "a familial abiotrophy of the optic nerve which may extend or be accompanied by degeneration in other parts of the central nervous system."

SIMON, Worcester, Mass. [ARCH. NEUROL. & PSYCHIAT.]

THE HYPOTHALAMUS. A. L. MCGREGOR, South African M. J. **14**:415 (Nov. 9) 1940.

The hypothalamus is an organ of control and coordination of the more primitive bodily and psychic functions. There are two distinct mechanisms active in the

hypothalamic region: one in the posterior portion, which produces a coordinated response of numerous sympathetic reflexes, and the other in the anterior portion of the region, which produces a similar coordinated response of parasympathetic reflexes. Each of these coordinated responses seems to be directed toward the maintenance of a constant internal environment. It is concerned not only with the elements of the "internal environment," such as the body temperature, metabolism, sleep and growth, but with the primitive reactions of the organism to the external environment, such as defense, aggression and fear, and with the perpetuation of the species, insured by sexual emotion and functional activity. The hypothalamus is frequently affected directly or indirectly by a variety of pathologic processes. The commonest symptoms referable to the hypothalamus are (1) obesity, (2) amenorrhea, (3) diabetes insipidus, (4) glycosuria and (5) sleep disorders; other symptoms are (1) cachexia, (2) sexual disorders, including premature sexual, as well as bodily and sometimes mental, development (pubertas hypothalamus), (3) disorders of thermal regulation and (4) ulceration of the upper part of the alimentary tract.

GONCE, Madison, Wis.

ASEPTIC MENINGITIS RESEMBLING PURULENT MENINGITIS AND FACIAL PARALYSIS FOLLOWING ACUTE SUPPURATIVE OTITIS MEDIA. P. NOBÉCOURT and E. ROSENKOVITCH, Bull. Soc. pédiat. de Paris **37**:458 (Jan.) 1940.

A 7½ year old boy had acute suppurative otitis media. After myringotomy there was a purulent discharge for a few days. Facial palsy and purulent meningitis developed. No bacteria were demonstrated in the spinal fluid. He was treated with sulfanilamide. The pathogenesis of the meningitis is discussed and the opinion is expressed that it was probably caused by a neurotropic virus and was not related to the middle ear infection. Sulfanilamide is given no credit for the boy's recovery because this type of meningitis usually clears up spontaneously.

BENJAMIN, Montreal, Canada.

A CASE OF PRIMARY PNEUMOCOCCIC MENINGITIS IN AN EIGHTEEN MONTH OLD INFANT. E. HURMUZACHE and D. G. POPOVICI, Bull. Soc. de pédiat. de Iasi **10**:39, 1939.

The child under question had been in a foundling's home since the age of 20 days. He had had generalized pyoderma, pneumonia, whooping cough with a second attack of pneumonia and then a third attack of pneumonia three months prior to the sudden development of pneumococcic meningitis. On the second day of the last illness 20 cc. of cerebrospinal fluid was removed and 10 cc. of an azosulfamide solution injected into the spinal canal. An equal quantity of the drug was given intramuscularly, and 40 cc. of antipneumococcus serum was administered intramuscularly. The child died the same day. The case is reported as one in which administration of one of the sulfanilamide drugs was of no avail.

LESLIE, Evanston, Ill.

ADRENAL INSUFFICIENCY IN EPILEPSY. E. CANTILO, Prensa méd. argent. **27**: 2641 (Dec. 18) 1940.

Cantilo states that chronic adrenal insufficiency in the absence of any other pathologic factor may be the cause of epileptic crises of the type of essential epilepsy or its equivalents. The condition is symptomatic for adrenal insufficiency and can be controlled by proper endocrine therapy without bromides and barbiturates. Patients with this type of epilepsy have an asthenic body build, hyperpigmented skin, depressive temperament, hypoglycemia during fasting and diminished insulin tolerance. The blood sugar content and the insulin tolerance return to normal values if the epileptic crises are controlled by endocrine therapy. The author reports satisfactory results in 3 cases from administration of endocrine extracts in daily doses of 0.5 Gm. of extract of the anterior lobe of the hypophysis,

0.25 Gm. of extract of whole adrenal gland and 0.1 Gm. of extract of the thyroid. The extracts were administered by mouth. The patients received chorionic gonadotropin (pregnyl) in doses of 1 cc. containing 500 units of the principle every other day for the first two months of the treatment. In cases reported by the author, the blood sugar content and the insulin tolerance returned to normal values and the epileptic crises had been controlled up to the time of the report, for more than one year, without administering any other drug. The author believes that this type of epileptic crisis is due to sudden lowering of the blood sugar content, which is preventable by endocrine therapy.

J. A. M. A.

THERAPEUTIC EFFECTS OF ENCEPHALOGRAPHY ON EPILEPSY IN CHILDREN. I. SCHLEIER, Arch. f. Psychiat. **111**:200 (Jan.) 1940.

Schleier studied the beneficial effect of encephalography in 49 children suffering from epilepsy, all of whom were from 2 to 16 years of age. In all of them the effect was beneficial, as shown by a decrease in frequency of the attacks. It was found that the amount of air injected had no bearing on the effect. The severity of complaints following the injection was directly proportional to the therapeutic effect. The effect was most marked in the younger children and decreased markedly after puberty. It was not dependent on the lapse between the onset of the disease and the time of the encephalographic procedure.

MALAMUD, Worcester, Mass. [ARCH. NEUROL & PSYCHIAT.]

DETERMINATION OF EFFECT OF PHOSPHATASE IN THE CEREBROSPINAL FLUID. O. SEUBERLING, Deutsche Ztschr. f. Nervenh. **151**:220, 1940.

Phosphatases are ferments which are able to change organic compounds of phosphorus into inorganic compounds. Seuberling describes in detail a method for the determination of the total phosphatase content of the cerebrospinal fluid. Its action is determined by adding spinal fluid in a certain proportion to a standard solution of organic phosphorus. On one half of this mixture immediate determination of inorganic phosphorus is made. The other part of the mixture is incubated before examination. The difference between the two amounts of phosphorus found reveals the inorganic phosphorus which was liberated by fermentation. This difference is directly related to the amount of the phosphatases in the cerebrospinal fluid or to the action of these phosphatases.

ADLER, Boston. [ARCH. NEUROL. & PSYCHIAT.]

OCCURRENCE OF THE DYSTROPHIC, NEURAL AND SPINAL FORMS OF PROGRESSIVE MUSCULAR ATROPHY IN ONE FAMILY. IMRE STERN, Schweiz. Arch. f. Neurol. u. Psychiat. **45**:447, 1940.

Stern summarizes the evidence tending to support the view that neural muscular atrophy, spinal muscular atrophy and progressive muscular dystrophy all have a common pathogenesis. Developmental anomalies of the central nervous system are fairly common in cases of progressive muscular dystrophy, and in the families of persons suffering from this condition various forms of nervous and mental disease are of frequent occurrence. Of greater significance are cases in which the clinical picture does not conform to any one of the three principal types of muscular wasting. In this connection, details are given of a case of muscular dystrophy in which sensory changes in the feet and marked atrophy of the muscles below the knee on one side were suggestive of the neural form of muscular atrophy. More than one type of muscular atrophy has been encountered in certain families. The offspring of patients suffering with spinal muscular atrophy, for instance, may have progressive muscular dystrophy. Dystrophic muscular changes have been observed in cases of acute and chronic poliomyelitis, lethargic encephalitis, tabes dorsalis and cerebellar tumor. Similar changes have been pro-

duced experimentally by removal of parts of the sympathetic or parasympathetic nervous system. Clinical evidence is cited in support of the belief that diencephalic centers of the autonomic nervous system may be involved in cases of progressive muscular dystrophy.

Stern reports the cases of 3 siblings, each of whom had a different variety of muscular atrophy. The mother, the father and 3 other children in this family were physically sound. The first patient, a woman aged 25, had a neural type of muscular atrophy; the onset of weakness at the age of 8 years was preceded by an attack of influenza and was accompanied by pain and paresthesias in the feet. Fibrillary twitching was noted in the small muscles of the hands, but wasting was more pronounced in the muscles of the feet and legs. Although muscular atrophy was likewise more marked peripherally in the second case, that of a youth aged 19, involvement was more diffuse, and fibrillary twitchings were observed in the lower as well as in the upper extremities. The onset had occurred with weakness in the hands four years previously, and symptoms of bulbar palsy had subsequently developed. Atrophy and fibrillary twitchings were noted in the tongue; the tendon reflexes were sluggish, but pathologic reflexes were not elicited. The patient was believed to be suffering from spinal muscular atrophy. The third patient, a girl aged 8 years, had progressive muscular dystrophy of the facioscapulohumeral type of Landouzy and Dejerine. Weakness of the muscles of the shoulders had become apparent one year previously, and there was some involvement of the muscles of the back and hips, as well as of the left quadriceps femoris muscle. The tendon reflexes were normally active, and fibrillary twitching was not observed.

The 3 foregoing cases are believed to furnish additional proof not only of the intimate relation of the various myopathies to one another but of the neurogenic origin of progressive muscular dystrophy. The studies of Ken Kuré suggest that the primary lesion in all these cases is to be found in the sympathetic or the parasympathetic centers of the spinal cord. The type of muscular atrophy, according to this view, would be determined by the location and extent of the heredodegenerative process within the spinal cord.

DANIELS, Denver. [ARCH. NEUROL. & PSYCHIAT.]

AN ISOLATED LESION OF THE LOWER OLIVE IN A CASE OF MYOCLONUS EPILEPSY. OSCAR AMMERMANN, Arch. f. Psychiat. **111**:213 (March) 1940.

Ammermann reports a case of myoclonus epilepsy which started at the age of 9 years and after a chronic course led to increasingly frequent attacks and death. The anatomic examination showed as the only lesion a bilateral process in both lower olives. Such an isolated lesion has been reported previously in cases of this disease. Other reports have emphasized an extension of the changes to the dentate nucleus. The fact has been stressed that although these two centers are not connected by tracts they show marked similarities in structure and frequently are affected simultaneously. The olive-dentate system is particularly frequently involved in cases of myoclonia of the soft palate, and it is argued from this that the olives play a special role in disease of the extrapyramidal system.

MALAMUD, Worcester, Mass. [ARCH. NEUROL. & PSYCHIAT.]

TREATMENT OF CHOREA MINOR BY INTRALUMBAR INJECTIONS OF AUTOSERUM. H. BROEKEMA, Maandschr. v. kindergeneesk. **9**:177 (Sept.) 1940.

Intralumbar administration of autoserum to patients with chorea produces as good a therapeutic result as any other treatment usually employed. Unlike almost all other treatments, autoserotherapy is absolutely without danger. It may even be successful when other means have failed. A summary of the most important methods of treatment and of their dangers is given. The theory of the action of serum injections is briefly discussed. VAN CREVELD, Amsterdam, Netherlands.

Psychology and Psychiatry

TEN "GOOD" EATERS AND TEN "POOR" EATERS: DEVELOPMENTAL BACKGROUND AND BEHAVIOR RELEVANT TO NUTRITION AND HEALTH OF A GROUP OF NURSERY SCHOOL CHILDREN. JEANETTE B. MCCAY and HELEN D. BULL, J. Pediat. **17**:230 (Aug.) 1940.

Twenty children from a nursery school group were selected for study. The basis of selection was the eating behavior at the noon meal during the first month of school. Ten of the children classed as "good" eaters were compared with a similar number of "poor" eaters. It was found that efficiency in eating was also an indication of development in other aspects. The birth weight of the "poor" eaters was smaller, the weight at the nursery school age was lower, the tissue tone and muscle tone were inferior and there was also a greater tendency toward anemia, poorer coordination of the eyes, lower rating in mental tests and more digestive disorders than among the "good" eaters. The "good" eaters showed a tendency to eczema, more pronounced enuresis and more frequent colds. Physical examination at entrance to nursery school revealed little difference in bony structure or posture. The amount of time absent from school due to illness was practically the same in the two groups. The amount of sleep in twenty-four hours was similar, although the "poor" eaters took shorter daytime naps but more rest at night. The "poor" eaters tended to gain about equal poundage with the "good" eaters during the school year. There were definite differences in the home environment of the two groups. There were more food dislikes and inexperience with common foods and more time spent over small meals by the "poor" eaters. More time spent out of doors, earlier nap times and quicker going to sleep at nap time were found among the "good" eaters. In addition, the "good" eaters were kept at home fewer days than the "poor" eaters for reasons not related to health.

RAUH, Cincinnati.

PSYCHOMOTOR FUNCTION IN DEVELOPMENTAL DISTURBANCES OF SPEECH. F. GREWEL, Maandschr. v. kindergeneesk. **10**:91 (Dec.) 1940.

In a number of children with retarded development of speech an important disturbance in the development of the motor function has been demonstrated by means of the motometric tests of Oseretzky. The retarded development of the articulatory ability is thus regarded as a consequence of general developmental retardation of motor function, and the same holds true to a still higher degree for hearing and muteness. This same general developmental retardation of motor functions is also found in various other conditions in which speech is retarded. In children with debility who have analogous defects the motor functions are disturbed to a larger extent than the intellectual functions.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of the Genitourinary Tract

CONGENITAL ANOMALIES OF URINARY TRACT IN CHILDREN AND INFANTS AND THEIR RELATION TO CHRONIC PYURIA. I. H. ERB and PEARL SUMMBERFELDT, Canad. M. A. J. **44**:14 (Jan.) 1941.

"1. In a series of 1,148 consecutive autopsies 51, or 4.4 per cent, revealed some form of congenital anomaly of the urinary tract. In 7 others, making a total of 58, or 5.05 per cent, dilatation of some part of the urinary tract with stasis was found, without a congenital lesion. Males predominated in the proportion of about 2 males to 1 female. Over 67 per cent occurred in children under 1 year of age.

"2. Anatomical changes, such as hypertrophy and trabeculation of bladder wall, hydroureter with ureteral angularity, hydronephrosis, and hydronephrotic atrophy

were present in 33 cases. These changes were interpreted as being secondary to obstruction from the congenital anomaly in 26 cases, to neuromuscular dysfunction in 4 cases, while in 3 cases no adequate cause was found. The most common obstructive anomalies were valves in the posterior urethra or ureters, stenosis at the uretero-pelvic or uretero-vesical orifices, or pressure from an aberrant artery.

"3. Inflammatory changes, as recognized by clinical pyuria or by the finding of pus in the urine at autopsy, were present in 25, or 43 per cent, of the cases. . . . 20 of the cases showing obstruction were free from infection. . . .

"4. Functional disturbances . . . may be due primarily to the anomaly itself or secondarily to the anatomical changes resulting from obstruction or to a superadded infection."

MOORE, Omaha.

URINARY TRACT INFECTIONS. T. R. MONTGOMERY, Northwest Med. **39**:243 (July) 1940.

Management of infections of the urinary tract in children is essentially the same as that of similar infections in adults. Sulfanilamide is given in a dose of 10 grains per 20 pounds (0.65 Gm. per 9.1 Kg.) of body weight and has as advantageous an effect on children as on adults. Mandelic acid may conveniently be given, 1 Gm. of the drug for every hundred cubic centimeters of urine excreted in twenty-four hours. If response to the treatment is not prompt a complete urologic investigation should be made.

ROBERTSON, Omaha.

RENAL LITHIASIS IN THE INFANT. WALDYR DE ABREU, J. de pediat. **6**:123 (April) 1939.

A case is reported in which renal lithiasis occurred in a child 3 years 2 months of age. After a clear discussion of the etiology, symptomatology, clinical forms, evolution, pathology and diagnosis of the condition, the author considers the treatment to be followed. He recommends early surgical intervention, especially when hematuria and acute pain are present. He believes that pyelotomy, nephrectomy or nephrotomy are the procedures to be used, the type of operation being determined by the degree and the cause of the lithiasis. Immobility of the calculus (or calculi), as evidenced in serial roentgenograms, should make one incline toward the more radical procedures.

SOTO, Habana, Cuba.

CHRONIC, OR LIPOID, NEPHROSIS. T. HALBERTSMA, Maandschr. v. kindergeneesk. **10**:1 (Oct.) 1940.

A case of nephrosis in a girl of 10 years who died of recurrent pneumococcic peritonitis after an observation period of two years is described. Necropsy disclosed changes characteristic of lipoid nephrosis, but there were also slight changes in the glomeruli and interstitial spots of inflammation.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of the Ductless Glands, Endocrinology

EFFECTS OF ANTERIOR PITUITARY PREPARATIONS IN EXPERIMENTAL PANCREATIC DIABETES. O. H. GAEBLER and HARRY W. GALBRAITH, Endocrinology **28**:171 (Feb.) 1941.

The relation of the diabetogenic and growth-promoting effects of preparations of the anterior lobe of the pituitary is not clear, although the fractions which have the greatest effect on growth are also the most diabetogenic.

It was previously shown that a single large injection of a preparation of the pituitary containing the growth-promoting factor causes only growth effects

(increase in weight and nitrogen storage) in normal and in phlorhizinized animals, whereas in depancreatized, insulin-treated animals it produces diabetogenic effects. It seemed possible that diabetogenic effects in the former were prevented by increased secretion of insulin.

A series of experiments on bitches to test this assumption indicated that the growth effects could not be attributed to the overproduction of dextrose from fat, that the increase in glycosuria was caused by interference with the utilization of dextrose formed from protein and that an increase in insulin output is apparently not the immediate and only cause of the nitrogen storage produced by the growth-stimulating preparation, but may be an essential condition for it.

JACOBSEN, Buffalo.

INCREASED FAT AND DECREASED CARBOHYDRATE APPETITE OF PANCREATECTOMIZED RATS. CURT P. RICHTER and EDWARD C. G. SCHMIDT JR., Endocrinology **28**:179 (Feb.) 1941.

Pancreatectomized rats allowed to select their own diets manifested a marked appetite for fat and ate little or no carbohydrate.

"So long as these pancreatectomized rats remained on the self-selection diet and were thus able to regulate their own diet, diabetic symptoms did not appear. However, when they were placed on the McCollum diet, 5 of the 8 rats showed a polydipsia, increased food intake, reduced rate of gain of weight and hyperglycemia.

"Thus, by their dietary selections the rats helped to correct the diabetic symptoms. Their selections agree closely with our knowledge of the needs of human diabetics."

JACOBSEN, Buffalo.

BEHAVIOR AND ENDOCRINE REGULATORS OF THE INTERNAL ENVIRONMENT. CURT P. RICHTER, Endocrinology **28**:193 (Feb.) 1941.

Claude Bernard first stated the principle of constant internal environment, which every living organism strives to maintain. Experiments on rats have demonstrated the ability of animals to regulate their food and water intake to their internal needs under a great variety of normal and pathologic conditions. When experimental diabetes insipidus is produced in an animal it drinks an increased amount of water in an effort to maintain a constant internal environment by compensating for the polyuria, which is primary. When either the anterior lobe of the pituitary or the thyroid, glands which constituate the chief regulators of the body temperature, is removed from a rat it builds an enormous nest in an effort to maintain constant body temperature. When the adrenal glands are removed from a rat, a procedure which causes an increased loss of sodium in the urine, it will consume five to twenty times the usual amount of sodium chloride to keep itself free from symptoms of insufficiency. Similarly, when the parathyroid glands are removed some animals will consume twenty times as much calcium as before operation to keep themselves alive and free from convulsions. Pancreatectomized animals eat a high fat, low sugar diet, which keeps them free from symptoms of diabetes.

Similar instances of self regulation of diet in human beings have been noted.

JACOBSEN, Buffalo.

COMPARATIVE BIOLOGIC RESPONSES TO THE INTERNATIONAL STANDARD AND COMMERCIAL CHORIONIC GONADOTROPINS. O. W. BARLOW and K. D. SPRAGUE, Endocrinology **28**:203 (Feb.) 1941.

The various methods of assaying chorionic gonadotropins are evaluated, and the results of tests on a number of commercial products are given.

It is concluded that because of increased stability estrogen in powdered form is superior to that in solutions.

JACOBSEN, Buffalo.

THE GROWTH STIMULATING EFFECT OF SMALL DOSES OF TESTOSTERONE PROPIONATE IN THE CASTRATE ALBINO RAT. H. S. RUBINSTEIN and M. L. SOLOMON, Endocrinology **28**:229 (Feb.) 1941.

Castrated rats treated with testosterone propionate grew faster than untreated castrates. It is suggested that testosterone propionate may possess an inherent growth-stimulating quality which strikes specifically at the accessory sex organs and more generally at other somatic tissues. There is a possibility that this androgen in small dosage may stimulate the growth function of the pituitary gland.

JACOBSEN, Buffalo.

STUDIES ON PITUITARY IMPLANTS AND EXTRACTS IN ADRENALECTOMIZED RATS. FREDERICK E. EMERY and LIDA G. GOTTSCH, Endocrinology **28**:321 (Feb.) 1941.

Implants of the pituitary gland of castrated rats kept adrenalectomized female rats alive and growing at a rate above normal, whereas pituitary extracts were less effective and ovarian implants were not beneficial.

These authors have shown previously that secretion from the corpus luteum keeps adrenalectomized rats alive, and it is presumed that the growth-stimulating and other factors, in addition to the gonadotropic substance, produced by the implanted tissue help to induce the phenomenal growth that is observed.

JACOBSEN, Buffalo.

THE HYPERTROPHIED THYMUS. M. LANGLOIS, Union méd. du Canada **69**:699 (July) 1940.

Langlois presents the thesis that simple hypertrophy of the thymus may produce two syndromes: (1) digestive, with distress following feeding, occurring especially late in the afternoon, and (2) respiratory, with stridor or cyanosis. Roentgenographic examination in cases of suspected hypertrophy of the thymus showed, surprisingly, that in 65.7 per cent the mediastinal shadow was enlarged. In all of these cases three roentgen treatments were given, with amelioration of the symptoms in every case.

DAFFINEE, Boston.

THYMECTOMY IN TREATMENT OF GENERAL ASTHENIA WITH RETARDED GROWTH. R. LERICHE and A. JUNG, Presse méd. **48**:681 (Aug. 28-31) 1940.

A girl 17 years of age was studied thoroughly to determine the cause of her extreme fatigability. Her growth was retarded. Although roentgen examination revealed no sign of an enlarged thymus, persistence of the thymus was suspected. With the use of local anesthesia, the thymus was removed. The gland weighed 25 Gm. and showed histologic signs of overactivity.

After operation the patient became more active and gay and did not complain of fatigue. A year later she appeared to be developing normally.

DAFFINEE, Boston.

Diseases of the Eye

TRANSMISSION OF SWIMMING-BATH CONJUNCTIVITIS TO MONKEYS. L. A. JULIANELLE, Am. J. Ophth. **23**:554 (May) 1940.

After discussing the methods and conditions of his study of the transmission of swimming bath conjunctivitis in monkeys, Julianelle gives the following summary and conclusions:

"1. Swimming-bath conjunctivitis may be transmitted experimentally to monkeys (M. rhesus). 2. The experimental infection appears as a follicular conjunctivitis following an incubation period of a week or more, and it may last for several

months. 3. The experimental disease is indistinguishable from experimental trachoma and experimental inclusion blenorrhea in the same animal. 4. The infectious agent of swimming-bath conjunctivitis is filterable under appropriate conditions through collodion membranes measuring 0.65 μ. A. P. D. [average pore diameter 0.65 micron]. 5. Since bacteriologically sterile filtrates of the human tissues retain their specific infectivity, the infectious agent is considered to be a virus. 6. No evidence was obtained of the existence of mutually protective immunity between experimental trachoma and experimental swimming-bath conjunctivitis. 7. The interrelationships of the inclusion-bearing diseases of the conjunctiva are discussed in brief."

W. S. REESE. [ARCH. OPHTH.]

PHLYCTENULAR CONJUNCTIVITIS: QUANTITATIVE DETAILS OF DESENSITIZING TREATMENT IN SIXTEEN CHILDREN. PHILIP J. HOWARD, J. Pediat. **17**:185 (Aug.) 1940.

The method and results of treatment of 16 children from 2 to 11 years of age suffering from phlyctenular conjunctivitis as one manifestation of a tuberculous process are recorded. In each case the smallest amount of tuberculin to which the child had an intradermal reaction was determined, and desensitizing injections were then started in amounts below this. When reactions were encountered, either locally at the site of injection or at the focus of infection or generally, indicated by a rise of temperature, the amount of tuberculin was lowered. In most cases the acute inflammation in these acute conjunctival irritations subsided in from three to six weeks, and in nearly all cases the patients progressed to a state of good vision.

RAUH, Cincinnati.

RETINITIS PIGMENTOSA. E. CUNNINGHAM DAX, Quart. J. Med. **9**:263 (Oct.) 1940.

Dax describes 11 cases of retinitis pigmentosa and states:

"Skeletal abnormality and deformity, melanosome-dispersion in the frog by specimens of blood and urine, headache, hyperthermia, hypogenitalism, hypercholesterolaemia associated with obesity, diminished glucose tolerance, disturbances of the water-salt metabolism, lymphocytosis, and diminished vitamin C excretion are amongst the abnormalities found which are common to several cases."

BRADFORD, Rochester, N. Y.

LENTICULAR REGENERATION (FORMATION OF LENTOIDS) IN SECONDARY CATARACT IN A FAMILY WITH HEREDITARY PERINUCLEAR CATARACT. F. RIEDL, Klin. Monatsbl. f. Augenh. **103**:169 (Aug.) 1939.

In an exhaustive paper the author reports on a family with hereditary perinuclear cataracts in five generations. Eight members were afflicted, 5 of them in the last two generations; their cataracts had been extracted elsewhere. Detailed case histories are given. The eyes operated on showed peculiar spheroid, irregularly shaped or conic formations in the secondary cataracts, and 3 of these patients had minute yellowish or brownish globular formations on the iris. Similar bodies, forming clusters, were noted in the corneal operative scars of 2 patients and in the vitreous of another. No histologic relation existed between these formations and the secondary cataracts. The number of these bodies varied between fifty and one hundred in the divers eyes. A number of photomicrographs prove the similarity with normal lens fibers. These lentoids originated from the epithelial cells of the lens. It is possible that the lentoids on the secondary cataract and on the surface of the iris originated from epithelial lenticular cells which escaped into the anterior chamber during discission. It may be, on the other hand, that these epithelial cells became detached from the secondary cataracts after several years, as the lentoids were discovered several years after discission. Formation of lentoids appears to occur rarely. Only Thiel and Handmann have published papers on this phenomenon.

K. L. STOLL. [ARCH. OPHTH.]

ZONULAR CATARACT AND SPASMOPHILIA. E. GSCHEIDEL, Klin. Monatsbl. f. Augenh. **103**:194 (Aug.) 1939.

The author examined at the Children's Hospital of the University of Tübingen 70 children who had been treated previously for spasmophilia and whose ages ranged between 1 and 17 years. He found the phosphorus content of the blood normal or slightly lowered and the calcium content lower than normal. Of the 140 lenses, 77 were perfectly clear; in the others, dotted, linear or feathery opacities were noted in the cortex. Opacities on the posterior pole of the lens occurred in 1 child, anterior embryonal cataract in 3 and linear opacities in the nucleus in 3. Zonular cataract was discovered in none of these 70 children with manifest spasmophilia, who had been under clinical observation for long periods. The author, therefore, concludes that spasmophilia has no influence on the formation of zonular cataract.

K. L. STOLL. [ARCH. OPHTH.]

CIRCUMSCRIBED MELANOSIS AND PIGMENTED NEVI OF SURFACE OF CORNEA. A. PILLAT, Klin. Monatsbl. f. Augenh. **104**:39 (Jan.) 1940.

The author reports on 4 cases of superficial, circumscribed melanosis of the cornea and on 1 case of a pigmented nevus in the cornea. Unlike nevi, the deposits of melanosis are flat pigmentations in the corneal epithelium; they may be linear, triangular or sector shaped, extending from the limbus for a few millimeters into the cornea or even to the center of an otherwise clear cornea. The remaining parts of the eye show no abnormal pigmentation. The form, color and extent of the melanotic deposits remained unchanged during extended observation. Their origin in the cornea, which contains no blood vessels, is due to formation of melanin in the melanoblasts, independently of the presence of blood and lymph. No impairment of vision was noted in these cases.

K. L. STOLL. [ARCH. OPHTH.]

MELANOSARCOMA OF THE EYE IN MORE THAN ONE MEMBER OF A FAMILY. P. J. WAARDENBURG, Nederl. tijdschr. v. geneesk. **84**:4718 (Nov. 30) 1940.

To the observations recorded in the literature on the occurrence of melanosarcoma in more than one member of a family, the author adds a case in which the growth arose in the anterior uveal segment of the right eye of an uncle and a niece; the diagnosis in the second case was made after an interval of fifteen years.

VAN CREVELD, Amsterdam, Netherlands.

OPHTHALMOLOGIC SIGNIFICANCE OF THE VITAMINS. H. WEVE, Nederl. tijdschr. v. geneesk. **84**:4996 (Dec. 21) 1940.

In this clinical report a short survey is given of the significance of the results of recent studies on the vitamins for ophthalmology in general and for the prevention and cure of certain diseases of the eye in particular.

VAN CREVELD, Amsterdam, Netherlands.

Skin Diseases; Allergy

THE PLACENTAL TRANSMISSION OF ANTIBODIES IN THE SKIN SENSITIVE TYPE OF HUMAN ALLERGY. WILLIAM B. SHERMAN, STANLEY F. HAMPTON and ROBERT A. COOKE, J. Exper. Med. **27**:611 (Nov.) 1940.

The authors report that a comparison of 12 maternal and 12 corresponding cord serums by the method of passive transfer showed the human placenta to be impermeable to skin-sensitizing antibodies. Direct cutaneous tests and passive transfer studies of 6 infants at the ages of 3 to 6 months showed negative reactions to the antigens to which their mothers were sensitive.

By these reactions there is demonstrated a difference between skin-sensitizing antibodies and the blocking antibody present in the serums of persons with hay fever, hemagglutinins and typhoid agglutinins, the placenta being permeable to the latter substances.

LYNCH, St. Paul. [ARCH. OPHTH.]

ERYTHEMA MULTIFORME BULLOSUM WITH INVOLVEMENT OF THE MUCOUS MEMBRANES OF THE EYES AND MOUTH (STEVENS-JOHNSON DISEASE). HARRY AGELOFF, New England J. Med. **223**:217 (Aug. 8) 1940.

The case of a 4 year old white girl is described in detail.

The patient was given a course of azosulfamide, 40 grains (2.59 Gm.) a day for nine days, the eyes were washed frequently with boric acid solution and 1 per cent gentian violet was applied to the cutaneous lesions. Several drops of a 1:2,500 solution of metaphen were instilled into the eyes three times a day, and later butyn sulfate–metaphen ointment was used. Eighteen hundred milligrams of vitamin B complex and 25 mg. of vitamin C were administered daily, Sedatives were given liberally. The child recovered in three weeks, and on discharge faintly pigmented areas were the only remaining evidences of the lesion.

Stevens and Johnson, in 1922, described this syndrome as that of an eruptive fever with stomatitis and ophthalmia. In the 9 cases described only 2 patients escaped total blindness, and these remained partially blind.

In only 1 of all the cases described, exclusive of the author's, did the disease occur in a girl; the patients ranged in age from 22 months to 16 years.

GENGENBACH, Denver.

PINK DISEASE TREATED BY WHEAT GERM. G. FORSYTH, M. J. Australia **1**:78 (Jan. 18) 1941.

Forsyth reports 3 cases of acrodynia in which prompt cure occurred with the administration of wheat germ (bemax) in the amount of 3 ounces (89 cc.) daily.

GONCE, Madison, Wis.

MELANOBLASTOSIS CUTIS LINEARIS S. SYSTEMATISATA. W. L. L. CAROL and D. J. H. BOUR, Maandschr. v. kindergeneesk. **9**:461 (Sept.) 1940.

A case of incontinentia pigmenti in a girl of 9 months is reported. After careful consideration the name of melanoblastosis cutis linearis s. systematisata was given to the disease. In some cells of the corium, which on other grounds were already regarded as melanoblasts, the dopa reaction (Bloch) was found to be positive. Other names which have been given to the condition are rejected by the authors. Typically in this condition at birth, shortly after birth or when the child is a few years old there appear pigmented spots in characteristic linear extension. The spots have a peculiar irregular form, are light to dark brown and are found especially on the trunk and extremities.

VAN CREVELD, Amsterdam, Netherlands.

Surgery and Orthopedics

MANAGEMENT OF PATHOLOGIC FRACTURES. E. M. BICK, Vido nueva **45**:378 (June) 1940.

The author reviews his observations on 85 fractures which occurred in 59 patients and stresses the importance of determining the underlying pathologic condition. The ages of the patients are not given, but some of the diseases discussed occur in childhood. In the discussion of osteogenesis imperfecta it is pointed out that because repair is relatively rapid the presence of the fractures should be recognized early so that realinement may be possible. Bick mentions the diminishing tendency to fractures displayed by patients with this disorder as they approach puberty. Five fractures in 3 rachitic patients are reported. Frac-

tures of the tibia and the vertebrae in 4 cases of Gaucher's disease are mentioned, and the author notes that there was delayed union in the instances of tibial fracture. In osteitis fibrosa cystica the author advises curettage of the fractured cyst. Two cases of osteomyelitis in which fracture occurred are included, and it is mentioned that normal repair ordinarily takes place with simple immobilization. Other cases included in the report are instances of fracture due to primary and metastatic tumors of bone.

DIETRICH, Beverly Hills, Calif.

CHRONIC, BURROWING ULCER TREATED WITH ZINC PEROXIDE. LAWRENCE J. COHEN, Bull. Hosp. Joint Dis. **2**:33 (Jan.) 1941.

A poorly nourished 10 year old boy had a large, unhealthy-looking ulcer on the inner aspect of the right thigh. It was of six years' duration and had occurred after an operation for suspected osteomyelitis. The application of various antiseptics had been unsuccessful, and curettage, resection and skin grafting had likewise produced no improvement. Contractures of the hip and the knee were present.

From material obtained from a sinus extending into the inguinal region, a microaerophilic streptococcus and a facultative Staphylococcus aureus haemolyticus were cultured. Since Mellanby has shown that zinc peroxide is almost a specific remedy for infections due to microaerophilic streptococci, because of the continuous liberation of oxygen from the substance, a preparation of zinc peroxide was introduced into the sinus daily and applied to the surface of the ulcer. Sulfanilamide was also given by mouth. Improvement was almost immediate, and complete healing was obtained within nine weeks. The contractures were overcome by continuous gentle traction. The original article should be consulted for the technic of the preparation and application of the zinc peroxide.

LESLIE, Evanston.

VOLKMANN'S ISCHAEMIC CONTRACTURE. D. L. GRIFFITHS, Brit. J. Surg. **28**:239 (Oct.) 1940.

This paper was given as a Hunterian Lecture to the Royal College of Surgeons and comprises a comprehensive review. Only 8 instances of Volkmann's ischemic contracture were observed in 21,000 cases of fracture at one clinic. Data from 32 cases in Manchester are tabulated. Two thirds of the patients were in the first decade, and all but 2 of the other third in the second decade of life. The author stresses the following signs: pain in the hand, cyanosis and swelling of the fingers, absence of the radial pulse and pallor of the hand. Evidence is produced in support of the theory that Volkmann's ischemic contracture is due to arterial injury and to the accompanying spasm of the collateral circulation. This view is supported by clinical signs of arterial occlusion in cases of both the acute and the chronic form of the disorder. Histologic examination shows muscle infarction. The theory that the contracture results from venous occlusion is rejected in view of the absence of any venous compression by hematoma in the acute form, the discovery of arterial lesions in operations at all stages of the disease, the occurrence of the contracture after arterial embolectomy and the production of the lesion in a small series of rabbits by arterial ligation. The early diagnosis of the lesion is discussed, and its prevention by operations designed to relieve arterial obstruction and collateral spasm is described.

KEITH, Toronto, Canada.

Teeth and Dentistry

HEREDITARY INFLUENCE MANIFESTED BY THE ABSENCE OF LATERAL INCISORS. J. REESE BEYRENT, J. Am. Dent. A. **28**:81 (Jan.) 1941.

A study of hereditary influence in the absence of lateral incisors is presented. In a family consisting of a mother and 12 children, 6 of the children had one or both lateral incisors missing. The father possessed both lateral incisors; the mother had neither. The 5 grandchildren had all incisors.

GEORGE PREWITT, Lexington, Ky. [ANGLE ORTHODONTIST]

AUTHENTIC DENTAL HEALTH INFORMATION FOR THE SCHOOL CHILD. J. M. WISAN, J. Am. Dent. A. **28**:401 (March) 1941.

Dental health information is being demanded by those concerned with the teaching of the child. This article discusses (1) the underlying theories and premises concerned with dental health practices that are consistent with present day scientific knowledge, and (2) what dental health practices the school child should adopt. GEORGE PREWITT, Lexington, Ky. [ANGLE ORTHODONTIST]

Miscellaneous

PEDIATRICS: ITS BROADER ASPECTS. OSCAR REISS, California & West. Med. **54**:119 (March) 1941.

This paper is a brief discussion of the mental hygiene aspect of pediatrics. The author states:

"If the pediatrician hopes to remain prominently in the picture, the scope of pediatrics must broaden to the point where its disciples attain a comprehensive understanding of every phase of child welfare, and qualify themselves as authoritative in all its aspects." DAVIS, San Francisco.

INHERITANCE OF GLUCOSE TOLERANCE. VERSA V. COLE, BEN K. HARNED and CLYDE E. KEELER, Endocrinology **28**:25 (Jan.) 1941.

The results of crossing a strain of rats having diabetic-like dextrose tolerance curves with a strain showing no evidence of low sugar tolerance were studied in detail. The various combinations of hypoglycemic genetic factors in the offspring are discussed. JACOBSEN, Buffalo.

A PRESUMPTIVE TEST FOR ORAL CONTAMINATION OF DRINKING UTENSILS. LEO A. DICK and G. J. HUCKER, J. Milk Technol. **3**:307 (Dec.) 1940.

Streptococcus salivarius was found on the lips of all of the subjects tested, and it was recovered from the rims of all the drinking glasses used by them. This organism survives for at least forty-eight hours on drinking utensils at room temperature. Rinsing in cold tap water may reduce the survival time of the organisms, but they can be recovered from the rims of all glasses so washed. It was shown that a washing in soapy water of 120 F. followed by a five minute rinse in water of 165 F. completely removed all the cocci.

In an examination of 100 eating places the highest incidence of contamination was found in bars, where only 3 per cent of the glasses were sterile. Soda fountains were the cleanest, their glasses showing only 80 per cent contamination. FLOOD, San Francisco.

THE ABSORPTION AND EXCRETION OF SULFAPYRIDINE AND OF SODIUM SULFAPYRIDINE IN MAN. HERMAN D. RATISH, ARNOLD DAVIDSON and JESSE G. M. BULLOWA, J. Pharmacol. & Exper. Therap. **69**:365 (Aug.) 1940.

Sulfapridine sodium is absorbed much more rapidly than sulfapyridine (2-[para-aminobenzenesulfonamido]-pyridine); a level of 4 to 6 mg. or more per hundred cubic centimeters of blood may be obtained within two and one-half hours when sulfapyridine sodium is administered, 5 Gm. being given at once and 1 Gm. every four hours day and night. With the administration of sulfapyridine sodium all of the patients (10) had levels of 4 mg. or more of the drug per hundred cubic centimeters of blood within two and one half hours, while this level was obtained only after twenty-four hours of administration of sulfapyridine.

Administration of sulfapyridine sodium by mouth in the dosage used caused no symptoms of irritation of the gastrointestinal tract other than nausea and vomiting. PILCHER, Cleveland.

Society Transactions

CHICAGO PEDIATRIC SOCIETY

Regular Meeting, Oct. 21, 1941

JAMES H. WALLACE, M.D., *President, in the Chair*

Influence of Drugs and Gases on the Secretion of the Mucosa of the Respiratory Tract. DR. FELIX P. BASCH (by invitation), DR. PAUL HOLINGER (by invitation) and DR. HENRY G. PONCHER.

The influence of various drugs and gases on the sputum and on certain properties of the tracheobronchial tree were studied by determination of physical and chemical properties of the sputum and bronchoscopic observations of the intrabronchial changes after therapy. The expectorant drugs ammonium chloride, potassium iodide, fluidextract of senega, ipecac and emetine hydrochloride liquefied the sputum consistently, as evidenced by a decrease in measured viscosity. On the basis of our determinations there is no difference in the efficiency of these drugs with regard to their ability to liquefy sputum. Inhalations of steam or of cool moisture liquefy the sputum more efficiently, through producing greater reduction in viscosity, than do the expectorant drugs. The content of organic and inorganic substances is also reduced. Thus the action is one of simple dilution. Inhalation of carbon dioxide acts as a most efficient expectorant. It reduces the amount of sputum within the bronchial tree by stimulating resorption and renders the remainder of the sputum more liquid, which permits it to be raised with more ease. Therefore, inhalation of carbon dioxide is entitled to definite status as an expectorant. The most efficient therapeutic regimen which may be instituted to clear the bronchial tree of its pathologic secretions has been found to be a judicious combination of inhalations of carbon dioxide and of moisture and use of expectorant drugs.

Regarding the influence on the sputum per se, inhalation of oxygen has been found to have an effect which retards the expectorant action; consequently, it may be considered an antiexpectorant, unless suitable measures are taken to counteract this effect. Oxygen increases the viscosity of the sputum greatly and likewise increases its content of solid substances. As a result, the sputum becomes not only thicker but more adherent to the mucous membrane. This undesirable influence of an otherwise very useful therapeutic procedure cannot be adequately compensated by the usual 5 per cent admixture of carbon dioxide. Only sufficient addition of moisture will equalize the observed disadvantage of oxygen inhalation. These results must be seriously considered in the therapeutic use of oxygen inhalation for patients with tracheobronchial pathologic conditions, particularly laryngotracheobronchitis. Codeine may also be considered an antiexpectorant, because it increases the viscosity of the sputum. Its use with an expectorant drug does not impair the expectorant action for the first twenty-four hours. After this, the viscosity of the sputum and its content of solid substances become gradually but definitely increased. Therefore, codeine must not be added to an expectorant if dilution and thinning of the secretion is the therapeutic objective desired. Atropine has been found to act as an antiexpectorant drug, through its action in decreasing the production of sputum and in causing a marked increase in the viscosity.

The future use of carbon dioxide is suggested as a therapeutic agent against pertussis, in which the most tenacious sputum is produced. It may also prove to be successful in the treatment of tracheobronchial irritation produced by certain

noxious gases used in industry or in modern warfare. And, finally, it could be effectively used to stimulate the cough reflex and increase the ease with which sputum is expectorated in cases in which pneumonia or tuberculosis is suspected.

DISCUSSION

DR. JULIUS H. HESS: I had the opportunity to follow this work during the eighteen months that it was carried on. It was a very practical clinical study. So brief a presentation in abstract form of a paper covering as much ground as this study covered hardly gives one a good idea as to the many ramifications of the problem in this largely unexplored field. Dr. Basch mentioned that many of the drugs that have been used on an empiric basis result in little more than liquefaction of the secretions of the bronchial tubes and alveoli. He believes, and I think rightly so, that they have little effect on the condition itself. I hope that in his discussion to follow he will dwell more in detail on the expectorant drugs in the treatment of his patients with chronic conditions.

This study was carried out largely with patients with chronic conditions who remained in the wards a long time, which offered a better opportunity for drawing conclusions than would a study of patients with acute disease seen in an outpatient department. I should like to emphasize a few of the points that have been made. Most physicians have used codeine and atropine alone or in combination in expectorant mixtures. I think that when one reads this paper one must acknowledge that these drugs have not much place in treatment of many types of chronic infection. As to the employment of moisture: Recently a cellophane cubicle was built in Sarah Morris Hospital, and some of the patients with acute infection were placed in this cabinet and steam turned in. I never realized before what an oppressive thing steam could be. When a cool spray was used the picture changed immediately for the better. Dr. Basch's suggestion that an oxygen–carbon dioxide mixture be used in combination with moisture gives possibly the best expression of what has come out of this very broad piece of work.

DR. M. P. BOROVSKY: I should like to ask Dr. Basch whether he has had any experience with medication such as benzoin with steam and, if so, whether any change in the action of the steam was noted. It has been common practice to use this, but if it has a desiccating influence on the mucous membranes it might be harmful. Another point is the use of helium, and I wonder if that has had any effect on the mucous membrane. It has been recommended for tracheobronchitis, and if it had the same effect as oxygen it would be undesirable.

DR. J. S. KRUGLICK: I should like to comment on what has been said on postural drainage. Two or three years ago a paper was given before this society on the importance of postural drainage in treatment of infections of the upper respiratory tract. Many of us used this type of treatment. Within a six months' period I saw numerous infections of the upper lobes of the lungs. Since I discontinued the use of postural drainage, the number of such infections that I have encountered has definitely decreased.

DR. FELIX P. BASCH: As Dr. Hess stated, my co-workers and I spent a great deal of time on this study, but still our contribution to the question of the influence of different drugs in different stages cannot be very large. There seems to be a distinction in the textbooks and in practical medical knowledge as to the action of expectorants in different stages of disease. Our method, unfortunately, did not give much opportunity for study of this particular phase. I can say only that expectorants are efficient and that, whatever they do, the viscosity is lowered by the group I mentioned. The resorption of sputum is also increased by the use of expectorant drugs. Therefore, the sputum which remains in the bronchi can be brought up more easily.

One drug, fluidextract of senega, is not much in favor because of the possible toxic influence on the blood. When dosage is judged carefully such an effect does not occur. One drop for each year of the patient's age given every three

or four hours is a fairly small dose but is sufficient in the long run. Emetine hydrochloride must not be given by mouth but must be injected, and it affects all parts of the tracheobronchial tree. In some cases of bronchiectasis we found plugs of secretion which could be brought out only by the bronchoscope or by postural drainage. We compared the properties of such plugs without treatment and after treatment, and, according to my memory, some of the drugs could even influence the qualities of this secretion, which usually remains inert. One of these drugs was emetine hydrochloride. Since it is known that moisture goes very deep in the bronchial tree and that a good deal of resorption takes place in the tracheobronchial tree, it is likely that the addition of drugs to the inhaled steam or moisture will have some effect. What helium might do to the bronchial mucosa I cannot say. I can say that Dr. Holinger's bronchoscopic findings after inhalation of carbon dioxide and oxygen have been a surprise to all of us. I therefore am rather reluctant to offer any statement as to the influence of helium on the mucous membrane before having seen it through Dr. Holinger's bronchoscope.

Immunization of Children Against Whooping Cough and Diphtheria: Preliminary Report. Dr. Louis W. Sauer and Dr. Winston H. Tucker (by invitation).

Bordet in 1936 reported on the injection of mixed diphtheria toxoid and Haemophilus pertussis vaccine. He in Belgium and Ramon and Debré in France gave three injections of mixed antigens three weeks apart.

Table 1.—*Percentage of Positive Reactions to Schick, Intracutaneous and Complement Fixation Tests After Three Injections of the Two Antigens Given Simultaneously*

	Schick Test	Cutaneous Test	Complement Fixation Test
St. Vincent's Hospital (1 week interval).....	16	85	88
Evanston Health Department Clinic (3 week interval).....	2	95	91

Table 2.—*Percentage of Positive Reactions to Schick, Intracutaneous and Complement Fixation Tests After Three Injections of the Two Antigens Mixed*

	Schick Test	Cutaneous Test	Complement Fixation Test
St. Vincent's Hospital (1 week interval).....	9	70	46
Evanston Health Department Clinic (3 week interval).....	3	91	73

Beginning in 1938, H. pertussis vaccine (15,000 million organisms per cubic centimeter) and diphtheria toxoid (plain) were injected either simultaneously (i. e. separately, at the same time, in the same arm), or mixed (i. e. in the same dose) into children at St. Vincent's Infant and Maternity Hospital and at the Evanston Health Department Clinic. At the former institution three injections of the two antigens were given at weekly intervals; at the latter, at three week intervals. For laboratory evidence of conferred immunity, Schick tests, determinations of the diphtheria antitoxin concentration of the serum and intracutaneous and complement fixation tests for pertussis were performed before and after the injections on a carefully controlled series of children in each of the four groups. At St. Vincent's Infant and Maternity Hospital the follow-up tests (retests) were per-

formed as a rule one week after the final injection; at the Health Department Clinic, as a rule two to three months after the final injection. Because practically no infant at the age when injections were made (between the eighth and the thirty-sixth month of life) had antibodies for diphtheria or pertussis before receiving the antigens, the preliminary tests were discontinued. Only the follow-up tests are now performed. The intracutaneous test usually gave a positive result in the immune, regardless of whether immunity followed the disease or treatment with vaccine. All whose blood failed to show a satisfactory complement fixation response were given an injection of 2 cc. of the plain H. pertussis vaccine; retests, especially for the children who had received injections at three week intervals, usually gave positive results.

Conclusion.—The immunization responses to the simultaneous and mixed injections of antigens compared favorably with those obtained after separate injection of the antigens. Ninety-eight per cent of the children who failed to show ample pertussis antibodies after the three injections at three week intervals responded to administration of a "stimulating" dose of 2 cc. of pertussis vaccine.

DISCUSSION

Dr. Winston H. Tucker: The question naturally arises as to the occurrence of reactions when the mixed antigens are injected as compared with that when pertussis vaccine and diphtheria toxoid are given in single doses at different times. In our experience there was generally a small amount of local reaction at the site of injection but systemic reactions with fever seldom occurred. We took pains that injections were made subcutaneously rather than intramuscularly; reactions are much less likely to occur when the subcutaneous route is employed.

During part of our study we compared the immunization response in children receiving the mixed antigens with that in a group of children who received pertussis vaccine and diphtheria toxoid at the same time but in separate injections. We found that there was no difference in the ability of the body to develop antibodies against both antigens, whether they were administered in mixed or in separate doses. From the viewpoint of the private practitioner, administration of two antigens in a mixed dose will decrease the number of visits required in routine protection of children against these preventable communicable diseases.

I should like to reemphasize the importance of a three week interval between injections. The antibody response appears to be best when this time interval is employed, as contrasted to periods of one or two weeks. We therefore suggest that pediatricians who are employing a one or two week interval for any immunization procedure change to the three week interval, with which much more satisfactory results will be obtained. We employed a stimulating dose of 2 cc. of plain pertussis vaccine for those children (about one fifth in our series) whose serum failed to show 3+ or 4+ complement fixation for pertussis three months after the three regular injections. After injection of the stimulating dose we found the pertussis complement fixation to become 3+ or 4+ in the blood of 98 per cent of the subjects. As it is known that all human beings gradually lose antibodies over a period of years, we suggest that private practitioners administer a stimulating dose of 1 or 2 cc. of mixed pertussis vaccine and diphtheria toxoid to children just before they enter school. The antibody response will be greatly stimulated, and this will play a large part in defense of the child in the frequent exposures to communicable diseases which occur during the early school years.

Dr. Henry B. Okner: What about the use of antigen or vaccine in active treatment? Dr. Sauer says two injections given a week apart are the same as one injection. Yet in active treatment it is recommended that the injections be given more frequently. It seems to me that there is an inconsistency.

Dr. Mandel L. Spivek: If the three week interval is the interval of choice in these immunizing procedures, the question comes up as to the routine use of

scarlet fever vaccine at weekly intervals. I wonder if Dr. Sauer has had any experience with three week intervals in immunization against scarlet fever and whether the one week interval is not the one to use for this.

DR. LOUIS W. SAUER: The intracutaneous test for pertussis as performed in this work usually gave a positive result in the immune, especially when the injections of antigens had been given at three week intervals. One part of the clear supernatant fluid (after prolonged centrifugation of 15,000 million bacilli per cubic centimeter of vaccine) was diluted with fifteen parts of 0.5 per cent phenol in 0.85 per cent sterile saline solution. When 0.1 cc. was injected intracutaneously, the reaction to the preliminary test was usually negative when observed twenty-four hours later. When the test was repeated from one to twelve weeks after the final injection of antigen, an erythematous area at least 10 mm. in diameter was usually observed twenty-four hours later, especially when the two antigens were injected at three week intervals.

The chief fault with the intracutaneous test was that it too often elicited a positive reaction (in approximately 25 per cent) in nonimmune subjects, i. e. in older infants who had had neither the disease nor the treatment with the vaccine. Flosdorf recently explained this on the basis of the presence of two toxins in the clear, supernatant fluid of potent vaccine.

Massive Dose Intravenous Arsenotherapy of Congenital and Acquired Syphilis in Infants and in Children. DR. I. MICHAEL LEVIN, DR. SAMUEL J. HOFFMAN and DR. DAVID KORANSKY.

The studies of Chargin, Leifer and Hyman during the past decade on intravenous massive drip arsenical therapy for syphilis focused attention on the possibility of applying this method to treatment of congenital and acquired syphilis in infants and in children. Such a method offered obvious advantages in eliminating a long-drawn-out course, technical difficulties of repeated injections, inadequate control of oral therapy and periods of lapse of treatment.

The problem is more complex than the treatment of adults, as the congenital syphilitic infant is in the late secondary or the tertiary stage of syphilis. The physical and nutritional developmental status must be carefully studied and corrected so far as possible before therapy is started. In this study, laboratory examinations were carried out prior to, during and following the five day course of treatment. These included serologic tests, complete blood counts, urinalyses and routine roentgenographic studies of the long bones. The patients were under close observation at all times, and treatment was interrupted when untoward symptoms occurred.

Three groups of patients were studied: (1) 14 infants under 6 months of age with manifest congenital syphilis; (2) 13 infants and young children between the ages of 6 months and 6 years, and (3) 4 children with acquired syphilis in the primary or secondary stage. None had previously received antisyphilitic therapy. At the beginning of the study we were concerned first with the development of a satisfactory technic for prolonged venoclysis and second with the determination of the toxicologic possibilities of massive intravenous arsenical therapy. Hence, a variety of patients was accepted in order to familiarize ourselves with the drug and with the technic.

For the first 11 patients, the dose was 1.6 mg. per pound (0.45 Kg.) of body weight per day. Absence of severe toxic reactions and failure to obtain rapid reversals of serologic reaction prompted increasing the dose to 2 mg. (9 patients), 2.5 mg. (9 patients) and 3 mg. (2 patients) per pound per day. On the first day of treatment half of the calculated daily dose was administered; on the second day, three fourths of the dose; and on the third, fourth and fifth days, one and one-fourth times the daily total dose. Laboratory studies made before, during and after treatment disclosed no evidence of any significant toxic reaction.

Reversal of serologic reaction occurred in the 4 patients with acquired syphilis; negative reactions have persisted for periods of five to eight months.

Of 8 infants 2½ months of age or less, reversal of serologic reaction was attained in 2 after nine months and two weeks respectively. Seven infants from 4 to 7 months of age failed to show reversal of the reaction, although in 2 the trend seemed favorable. Two were returned to the hospital after six months for a second course of treatment. Of 12 infants aged 14 months to 6 years, reversal of the serologic reaction occurred in 2, although whether this will persist is uncertain as yet. Clinically, all the patients showed improvement.

Conclusion.—No final conclusion is drawn from this preliminary study other than that massive dose intravenous arsenotherapy by the drip method is feasible in treatment of congenital and acquired syphilis in infants and in children. With care the technical difficulties of prolonged venoclysis can be overcome. The toxicologic reactions to mapharsen have thus far been minor.

It is felt that rising titers obtained in quantitative Kahn tests six months after treatment are indicative of failure and that a second course of therapy should be given; the possibility of increasing the dose on repetition of treatment is to be determined.

The implications of observations so far are encouraging; detailed studies will be reported in the future.

DISCUSSION

DR. S. J. HOFFMAN: A few years ago a detail man asked me if he might take some photographs of rachitic children. The next day he came with a retinue of photographers, and to my surprise there was not a patient with rickets in the hospital. The same thing would be likely to be true of patients with syphilis. Ten years ago one could always find 3, 4 or 5 patients with congenital syphilis in the wards; today if such a patient is admitted, interns, nurses and residents come to observe a bizarre situation. The practice of medicine is in a definite period of transition.

There is a great difference between congenital and acquired syphilis. In the acquired type there is more or less a line of demarcation between the primary lesion and the secondary stage, and one knows approximately when the tertiary lesion begins. With congenital syphilis there is a different problem. The physician may have under his care a newborn infant whose mother has been treated; frequently he does not know when she placed herself under antepartum care or when she came to the clinic; or he may have a newborn child of a treated or of an untreated syphilitic mother. The infant may show no evidence of syphilis. He is at a loss to know what to do in many instances. It is known that there may be a positive reaction carried over from mother to child. The infant must be observed for a long time, and frequently one does not know whether the child has syphilis or not. It is known, however, very definitely, that in the massive treatment of syphilis in adults the results are more favorable when treatment is given during the primary stage before the serologic reaction is positive than when it is given after the reaction has become positive. The results are not so satisfactory when patients are treated in the secondary stage.

In congenital syphilis one sees no primary lesion. How, then, can one detect congenital syphilis as early as possible? My associates and I have this in mind. With the cooperation of the obstetric department at Cook County Hospital, we intend to study the placenta and the cord of every mother who has been treated for syphilis or who has a positive serologic reaction when she comes for delivery. We feel that if one can find syphilitic changes in the placenta or in the cord or can demonstrate spirochetes with proper staining the disease can be nipped in the bud and treatment should be started immediately. The few months that may elapse while diagnosis is being considered are valuable, and if treatment is not begun promptly one may have to deal with a tertiary stage rather than with a late secondary one.

The other thing we expect to do is to compare the titers of the Kahn test of the mother and of the child on the third postpartum day. If the mother has 30 or 50 Kahn units and the child has 400 or 500, that is presumptive evidence of syphilis in the infant. At one time we thought we knew something about roentgen rays, but since Caffey and Aries reported their work we are more confused than ever. We do not know what syphilis of the bone is, with the exception of a couple of definite findings. The rationale of the massive five day treatment I think is clear. At the exhibit of the United States Public Health Service at the meeting of the American Medical Association, 143 physicians reported deaths from the accepted routine therapy for syphilis. I have often wondered what happens if one gives an infant an injection of an arsenic compound and then waits a week to give the second injection. Do the spirochetes remain quiescent, or do they continue to multiply and do their usual damage? The only treatment that I feel approaches the five day treatment with mapharsen is daily oral administration of acetarsone by mouth. One knows then that the drug is attacking the spirochetes constantly.

The essence of our paper is the recommendation to diagnose congenital syphilis as soon as possible and start treatment immediately. If the diagnosis is doubtful, one should institute the five day treatment. Infants tolerate the drug very well and with minimal danger. Those few valuable months that one loses while making up one's mind as to the diagnosis are extremely important to the future of the infant.

Dr. Herbert Rattner (by invitation): During the past year in the department of dermatology at Cook County Hospital my associates and I have treated 270 patients with early syphilis by means of the five day massive dose technic. Among them were 4 patients who were 16 years of age or under; and I lean heavily on these 4 patients for license to appear before this select body tonight. We administer to each patient daily, regardless of age, sex or weight, 0.24 Gm. (240 mg.) of mapharsen dissolved in 2,000 cc. of 5 per cent dextrose solution. In five days a patient receives 1.2 Gm. (1,200 mg.) of mapharsen. Dr. Levin and his associates had to work out the dosage for their patients by themselves. In our series it was done for us by the originators of the method. The solution is administered in a vein of the hand and allowed to flow at the rate of about 40 to 50 drops per minute. No special preparation of the patient is necessary, but we have been careful to select only healthy persons. The experience is none too pleasant for the patients, nor is it a great hardship. Most of them suffer from headache, nausea, vomiting, fever and pain in the arm. In general the reactions are minor ones, but in 3 instances we have encountered alarming reactions. There were 2 patients with toxic encephalopathy and 1 patient in whom there developed acute glomerulonephritis, hepatitis, ileus and pericarditis. There have been no fatalities in our group.

The results of the treatment, so far as can be judged this early, have been satisfactory. The best results were obtained in the patients who reported for treatment very early. In those with chancres and negative serologic reactions, the incidence of "cures" was apparently 100 per cent. In those with late secondary eruptions the incidence dropped to about 87 per cent. We have retreated 12 patients, because of reinfection (2 undoubted cases), relapse or superinfection. Among our patients were 10 pregnant women with early syphilis, 5 of whom have given birth to apparently healthy infants, the oldest now 8 months of age. The other women are awaiting delivery.

The method, of course, is a radical departure from standard methods of treatment. The results in the first cases in which it was used in New York, in 1933, have been excellent. We have been encouraged because our early results are paralleling the results in the New York cases. Were it not for the cases of encephalitis that have occurred (1 in about every 200 cases) the method of treatment would be generally adopted. For the present it must still be considered as in the experimental stage, until more patients have been treated for a sufficiently

long time to allow statistics to tell the complete story. The study of Dr. Levin and his associates has been an excellent one and when completed will undoubtedly be a distinct contribution to the subject of syphilis in children.

DR. S. J. BENENSOHN: We at Cook County Hospital have been interested in the subject of pregnancy and syphilis for the past eight years and have had opportunity to treat a large number of patients. Treatment has been intensive, with no rest periods, beginning with graduated doses of neoarsphenamine and bismuth subsalicylate and continuing throughout pregnancy. I think our statistics show that congenital syphilis may be prevented by treatment of the mother if she can be treated early enough. It is generally accepted that a positive serologic reaction in an infant is not significant until about the eighth week of life; it takes approximately eight weeks for the reactive substances to disappear from the blood stream.

We feel that if pediatricians take into consideration the amount of therapy the mother has had during pregnancy it will be of assistance, in doubtful cases, in helping to decide whether a patient should or should not be treated. If the mother has had ten treatments and the infant presents questionable evidence of syphilis, I do not think that the infant need be treated, although it should be kept under observation. On the other hand, if the mother received inadequate therapy and the findings are questionable, it would be better to treat the infant unnecessarily than to overlook congenital syphilis. The serologic reactions during pregnancy are not always dependable. A patient may have negative reactions or very weak reactions to fixation tests during pregnancy and six weeks post partum have a markedly strong positive reaction. In the early days we did not treat patients with weak reactions, and many pregnancies terminated tragically. We now treat all such patients, regardless of the strength of the reaction, and our results have been much better. I think pediatricians who take care of children with congenital syphilis will be of much help if they insist that the mothers of these children continue treatment and that in every subsequent pregnancy they resume treatment.

DR. SAMUEL J. HOFFMAN: I take issue with Dr. Benensohn on one point. I think the Kahn test has value if the titer of the mother and that of the infant are compared. If the infant has 300 or 400 units and the mother has 20 or 30 units, I believe that is presumptive evidence that the child has syphilis.

Book Reviews

The Premature Infant: Its Medical and Nursing Care. By Julius H. Hess, M.D., and Evelyn C. Lundeen, R.N. Price, $3.50. Pp. 317, with 14 tables and 74 illustrations. Philadelphia: J. B. Lippincott Company, 1941.

No one is better qualified to discuss the practical aspects of medical care of premature infants than the senior author, because of his vast personal experience in the field. He is ably assisted in this task by Miss Lundeen, who displays the same intimate knowledge of the practical problems involved in the nursing care in this field. The title of the book is perhaps too broad and somewhat misleading. Incorporation of the subtitle into the main title, i. e., "The Care of the Premature Infant," would have reflected more accurately the contents and aims of the volume. The relative allotment of space in the text supports this opinion of the reviewer.

The first three chapters (22 pages) present rather cursorily the clinical evidences of immaturity of the different systems and organs and of the general underdevelopment exhibited by the premature infant. The brevity of this section is condoned only by its obvious intent: to give the reader a sufficient background to understand the physiologic basis underlying management. The following thirteen chapters (155 pages) are devoted to a detailed description of the essential elements constituting good postnatal care. The physical equipment needed to fulfil the minimal requirements of a nursery for the premature both in the hospital and in the home is fully and simply presented; the qualifications and duties of the nursing personnel are given; the relative merits of human milk and a variety of prepared cow's milk in feeding are briefly discussed in the light of the authors' extensive experience, and the technic of a number of the more common specific therapeutic procedures is described. In the next eleven chapters (78 pages) are contained short clinical surveys of some of the pathologic conditions most frequently seen in premature infants in early postnatal life, again with the main emphasis on treatment. The final two chapters (14 pages) review some of the existing community plans designed to cope with the problems of the premature infant and call attention to the generally favorable outcome of surviving infants who have received adequate postnatal care. An addendum (21 pages) supplements the main body of the book by presenting in tables and illustrations further details of practical management.

Although the statement is made in the preface that the text will present "something of the practical experience gained from work in the station coordinated with what medical science has to offer today," the paucity of published references (thirty-two references, of which five are devoted to pneumothorax) is not wholly consistent with the stated aims. The justifiable temptation to present in greatest detail the facets of the subject with which the authors are most familiar is also evident in a number of the sections of the book. For example, in the discussion of incubators, 6 pages are devoted to the Hess heated bed, while the same number of pages are given to all of the other incubators mentioned, and no mention is made of the survey of incubators made by the Children's Bureau and the Bureau of Standards. The same disproportion is evident in the chapter on oxygen therapy (chapter 16). Finally, a number of statements are categorically made which are, in the opinion of the reviewer, at least subject to doubt. Only a few examples need be cited. For example, on page 26 it is stated that "it is often advisable to put such a sick [full term] infant in the nursery for premature infants." Likewise, recommendation of frequent intramuscular injection of blood for prevention of hemorrhage, treatment of pneumonia or "to furnish nutrition and antibodies" can hardly be considered modern or established practice.

For physicians and nurses directly interested in the practical aspects of premature care, both in the hospital and in the home, this book supplies much invaluable information. It is obviously not intended for the student of physiology interested in the pathogenesis of the handicaps peculiar to the premature infant.

Breathing Capacity and Grip Strength of Preschool Children. By Eleanor Metheny. Pp. 207, with 7 illustrations and 14 tables. Iowa City: Univ. Iowa Press, 1940.

In the first section the reader is made familiar with the nature of the problem to be investigated, the material used for the investigation and the sort of data obtained therefrom. In order to learn the relation of breathing capacity (vital capacity) and grip strength to other physical and mental measurements and to health, it was necessary to devise apparatus which would be suitable for use with the 169 children, aged 2½ to 6½ years, available for this study in the Iowa Child Welfare Research Station.

The first chapters in sections II and III review the previous work done on breathing capacity and grip strength. The next chapters describe the devising of apparatus—spirometer and dynamometer—and the working out and checking of the reliability of technics. The remainder of each of these sections is taken up with the presentation and discussion of results with adequate charts and tables. Formulas are given for calculating either breathing capacity or grip strength from a child's height and age. Quotients are derived by dividing the actually determined figure times 100 by the calculated figure. Their significance is discussed.

The fourth section explores the field of possible relationships between the results of these tests and the health status of a given child or his incidence of "colds."

The newly devised apparatus—especially the dynamometer—appears to be both ingenious and sound. The work itself has been carefully done, and the analyses are accurate and interesting. This reviewer finds two serious objections to the work as presented. The first and less important complaint is that the monograph is unnecessarily wordy. There is a good deal of repetition—especially in section III—and parts of the discussions verge on "elaborations of the obvious." The second and more important complaint concerns a fundamental aspect of the investigation. It seems a shame that such interesting tests should have been administered over so brief a time when the investigation was being carried out in an institute conducting a longitudinal study of children. It seems improbable that any safe conclusions could be drawn concerning the relations between any single subject's breathing capacity or grip strength and his physical or mental characteristics, his growth or his health unless one repeated these tests at regular intervals through a significant portion of his whole span of growth. In this study only 37 children were retested, and the time interval between the first and the second test was not more than seven months. In the work on possible relations between the tests and the incidence of "colds" 20 children were tested daily from Nov. 15, 1939 to December 15 and 22 from Jan. 3, 1940 to February 23.

In spite of these shortcomings I believe that this monograph is worth reading and that it contains enough suggestive evidence of the value of these tests in early life to warrant further study of a longitudinal nature.

Complete Weight Reducer. By C. J. Gerling. Price, $3. Pp. 246. New York: Harvest House, 1941.

This unique reference book contains most if not all of the information needed by a patient for safe and effective reduction of body weight. It is composed in encyclopedic form, with short sections arranged alphabetically for easy reference. There are some hundreds of paragraphs, each discussing a related subject such as "Age and Diet," "Cabinet Baths," "Glandular Extracts," "Metabolism" and

"Standards of Weight" (with tables and rules), providing quick access to information concerning almost any phase of the reducing problem.

The contained material is intensely practical. The usual quantitative data regarding food, exercise and endocrine abnormalities are presented in a complete yet useful manner. There are many specific data regarding diet fads, reducing medicines, baths, catharsis and other dangers, all approached from a scientific basis which exposes the fallacies of the many existing fads. Convenient tables of nutritional values, work requirements, liquor composition and others are included.

The scientific attitude of the author is sensible. Only those measures with a sound basis in scientific fact are approved. Exposures of unsound practices are ruthless and unprejudiced. Unquestionably the patient or physician interested in weight control by sane methods will profit by owning and using this volume. If more of this type of material were in the hands of the laity instead of the usual literature of exploitation, methods of weight reduction would be much more safe and effective than those practiced at present.

Immunity Against Parasitic Diseases. By James T. Culbertson. Price, $3.50. Pp. 274, with 4 illustrations. New York: Columbia University Press, 1941.

In writing this book, the author has attempted to organize the voluminous literature which has appeared during the past twelve years in the field of parasitic immunity. This has been done with the dual purpose in mind of providing the beginning student with an introduction to the field and the experienced worker with a ready reference source. He admittedly assumes that the reader will be one who is well trained in both parasitology and immunology.

The subject matter is divided into three sections. In the first section the general principles of resistance and immunity, the mechanisms of specific immunity and the methods for demonstrating immunity are reviewed. In the second section specific diseases are discussed, with five chapters devoted to the protozoa, three to the helminths and one to the arthropods. The final portion is devoted to a brief discussion of applied immunologic measures, including a discussion of vaccination against parasitic diseases and immunologic methods of diagnosis.

The book is well printed and well edited. While this volume will be of limited interest to the average physician because of its specialized nature, the author has produced a complete and well organized review which will be an extremely useful reference source for workers in the field of parasitic immunity.

Mother and Baby Care in Pictures. By Louise Zabriskie, R.N. Second edition revised. Price, $1.50, cloth; $1.00, paper. Pp. 208, with 204 illustrations. Philadelphia: J. B. Lippincott Company, 1941.

Louise Zabriskie is field director of the Maternity Center Association of the city of New York. She was formerly night supervisor of the Lying-In Hospital of the same city. Her experience in direct care of the mother and baby and in helping the mother to meet the demands of pregnancy and to make ready for the care of the new baby gives her an excellent background for the book she has prepared. She knows not only what is important for the mother to know but also what questions will perplex her, where her interest in development lies and how it may be stimulated further. For these reasons this book with its plentiful excellent illustrations and clear text should prove a very satisfying one to parents, during both the prenatal period and early childhood of their offspring.

Diseases of the Blood and Atlas of Hematology. By Dr. Roy R. Kracke. Price, $15. Pp. 692, with 46 illustrations, 54 plates and 40 tables. Philadelphia: J. B. Lippincott Company, 1941.

The second edition of this work conforms to the excellent standard set by the previous edition. An entire section has been added on vitamin K, and new chapters on hemolytic anemias and hemoglobinuria. Other sections that have been

amplified are those on blood transfusion, blood banks and blood plasma. New material has been given on the action of drugs on the blood and fractionation of liver extracts and the porphyrin compounds. Omissions of certain phases of osteosclerotic anemia, achrestic anemia, ovalocystosis, Hodgkin's disease and histoplasmosis have been corrected.

With the addition of new color plates and illustrations, an excellent description of the diseases of the blood is contained in this one volume.

Estenosis hipertrofica del piloro en el lactante. By Carlos Ruiz. Pp. 79, paper. No illustrations. Buenos Aires: El Ateneo, 1940.

This monograph, written in Spanish, gives the etiology, pathology, histology, diagnosis and treatment of pylorospasm. The material has been gathered from 21 cases that the author has studied very thoroughly. Of particular interest are the determinations of the blood and plasma chlorides and of the alkaline reserve that were made before and after operation.

1942 Daily Log. Price, $6. Champaign, Ill.: Colwell Publishing Company, 1941.

The Daily Log for 1942 contains essentially the same material that it always has for efficient bookkeeping. Physicians are not good business men as a rule, and such a book as this is essential if they are to know what they are doing and what they are spending.

Directory of Pediatric Societies

INTERNATIONAL

International Association of Preventive Pediatrics

President: Prof. S. Monrad, Dronning Louises Børnehospital, Copenhagen, Denmark.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

International Congress of Pediatrics

President: Dr. Henry F. Helmholz, Mayo Clinic, Rochester, Minn.
General Secretary: Dr. Kenneth D. Blackfan, 300 Longwood Ave., Boston.
Assistant Secretary-Treasurer: Dr. Charles F. McKhann, University of Michigan, Ann Arbor, Mich.

Canadian Committee:
Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto.
Secretary: Dr. H. P. Wright, 1509 Sherbrooke St. W., Montreal.
Place: Boston. Time: Postponed indefinitely.

International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

FOREIGN

Argentine Pediatric Society of Buenos Aires

President: Dr. Martin Ramón Arana, 1809 Rodriguez Peña, Buenos Aires.
General Secretary: Dr. Alfredo Larguia, Cerrito 1179, Buenos Aires.

British Pediatric Association

President: Prof. Charles McNeil, 44 Heriot Row, Edinburgh, Scotland.
Secretary: Dr. Arthur G. Maitland Jones, 31A Weymouth St., London, W. 1.

Danish Pediatric Society

President: Dr. E. Lenstrup, Copenhagen.
Secretary: Dr. E. Gjørup, Dronning Louises Børnehospital, Copenhagen.

Nederlandische Vereeniging voor Kindergeneeskunde

President: Dr. J. H. G. Carstens, Servaasbolwerk 14ª, Utrecht, Holland.
Secretary: Dr. R. P. van de Kasteele, Laan van Poot 340, 's Gravenhage, Holland.
Place: Different places. Time: Three times a year.

Paediatrický Spolok na Slovensku

President: Dr. A. J. C. Chura, Lazaretská 11, Bratislava.
Secretary: Dr. P. Rados, Lazaretská 6, Bratislava.
Place: Pediatric Clinic, University Bratislava. Time: Six times a year.

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* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

ROYAL SOCIETY OF MEDICINE, SECTION FOR THE STUDY OF DISEASE IN CHILDREN

President: Dr. E. A. Cockayne, 98 Harley St., London, W. 1, England.
Secretary: Dr. R. Lightwood, 86 Brook St., London, W. 1, England.
Place: 1 Wimpole St., London. Time: Fourth Friday of each month, 4:15 p. m.

PALESTINE JEWISH MEDICAL ASSOCIATION, SECTION OF PHYSICIANS' OF CHILDREN'S DISEASES

President: Prof. S. Rosenbaum, 26 Bialikstr., Tel Aviv.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

SOCIEDAD CUBANA DE PEDIATRÍA

President: Dr. Clemente Inclan Costa, Marique 48, Habana.
Secretary: Dr. Serafin Falcon Lopez, Calle B No. 356, Velado, Habana.
Place: Cátedra de Clinica Infantil, Hospital Mercedes, Habana. Time: Last Wednesday of every month.

SOCIEDAD MEXICANA DE PEDIATRIA

President: Dr. Fernando López Clares, 12/a. Medellín 191, México City.
Secretary: Dr. Jesus Gómez Pagola, Versalles 64, Mexico City.

SOCIEDAD VENEZOLANA DE PUERICULTURA Y PEDIATRIA

President: Dr. Ernesto Vizcarrondo, Venezuela.
Secretary: Dr. E. Santos Mendoza, Venezuela.

SOCIÉTÉ DE PÉDIATRIE DE PARIS

President: Dr. B. Weill-Hallé, 49 Avenue Raymond Poincare, Paris, France.
Secretary: Dr. Jean Hallé, 10 bis Rue Pré aux Clercs, Paris, France.
Place: Hôpital des Enfants Malades, 49 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

URUGUAYAN SOCIETY OF PEDIATRICS

President: Dr. Conrado Pelfort, Av. 18 de Julio 1246, Montevideo.
Secretary: Dr. Héctor Mourigan, Ave. 18 de Julio 2175, Montevideo.

NATIONAL

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, SECTION ON PEDIATRICS

Chairman: Dr. Philip M. Stimson, 25 Claremont Ave., New York.
Secretary: Dr. Hugh L. Dwyer, 315 Alameda Rd., Kansas City, Mo.
Place: Atlantic City. Time: June 8-12, 1942.

AMERICAN ACADEMY OF PEDIATRICS

President: Dr. Edward C. Mitchell, 1073 Madison Ave., Memphis, Tenn.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Place: Palmer House, Chicago. Time: Nov. 4-7, 1942.
Region I. Place: Bellevue-Stratford Hotel, Philadelphia. Time: April 1-3, 1942.
Region III. Place: Hotel Cleveland, Cleveland. Time: May 14-16, 1942.
Region IV. Place: Ambassador Hotel, Los Angeles. Time: April 23-25, 1942.

AMERICAN HOSPITAL ASSOCIATION, CHILDREN'S HOSPITAL SECTION

Chairman: Dr. D. L. Richardson, 593 Eddy St., Providence, R. I.
Secretary: Dr. Joelle C. Hiebert, 299 Main St, Lewiston, Maine.

American Pediatric Society

President: Dr. Edwards A. Park, Johns Hopkins Hospital, Baltimore, Md.
Secretary-Treasurer: Dr. Hugh McCulloch, 325 N. Euclid Ave., St. Louis.
Place: Skytop Lodge, Skytop, Pa. Time: April 30–May 2, 1942.

Canadian Society for the Study of Diseases of Children

President: Dr. L. M. Lindsay, 815 Medical Arts Bldg., Montreal.
Secretary-Treasurer: Dr. Elizabeth Chant Robertson, Hospital for Sick Children, Toronto.

Society for Pediatric Research

President: Dr. George M. Guest, Children's Hospital, Cincinnati.
Secretary: Dr. Mitchell I. Rubin, 1740 Bainbridge St., Philadelphia.

SECTIONAL

Intermountain Pediatric Society

President: Dr. Eugene Smith, 385–24th St., Ogden, Utah.
Secretary-Treasurer: Dr. W. C. Cheney, 837 Boston Bldg., Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

New England Pediatric Society

President: Dr. R. Cannon Eley, 319 Longwood Ave., Boston.
Secretary-Treasurer: Dr. James Marvin Baty, 319 Longwood Ave., Boston.
Place: Boston Medical Library. Time: Four meetings a year, occurring from September to May.

North Pacific Pediatric Society

President: Dr. S. G. Henricke, 4215 N. E. Hancock St., Portland, Ore.
Secretary: Dr. J. S. Backstrand, 333 Wyatt Court, Salem, Ore.

Rocky Mountain Pediatric Society

President: Dr. Donn Barber, 802½–8th Ave., Greeley, Colo.
Secretary: Dr. Kenneth Schmidt, Republic Bldg., Denver.
Place: Children's Hospital, Denver. Time: First Saturday of each month from September to May, inclusive, 7:30 p. m.

Southern Medical Association, Section of Pediatrics

Chairman: Dr. Harvey F. Garrison, 319 E. Capitol St., Jackson, Miss.
Secretary: Dr. Warren W. Quillian, 227 Aragon Ave., Coral Gables, Fla.

STATE

Alabama Pediatric Society

President: Dr. M. V. Adams, 803 Government St., Mobile.
Secretary-Treasurer: Dr. William R. Britton, 4 Catoma St., Montgomery.

Arkansas State Pediatric Association

Chairman: Dr. C. B. Billingsley, 1425 N. 11th St., Fort Smith.
Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

California State Medical Society, Section on Pediatrics

Chairman: Dr. William Belford, 233 A St., San Diego.
Secretary: Dr. John J. Miller Jr., 2398 Sacramento St., San Francisco.

Florida State Pediatric Society

President: Dr. Warren W. Quillian, 227 Aragon Ave., Coral Gables.
Secretary: Dr. George N. Leonard, 605 Lincoln Rd., Miami Beach.
Place: Concurrent with state association meeting at time of convention.

Georgia Pediatric Society

President: Dr. R. C. McGahee, 1345 Greene St., Augusta.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St., N. E., Atlanta.

Hezekiah Beardsley Pediatric Club of Connecticut

President: Dr. Ernest Caulfield, 683 Asylum Ave., Hartford.
Secretary: Dr. Edward T. Wakeman, 129 Whitney Ave., New Haven.
Time: Three meetings a year.

Illinois State Medical Society, Section on Pediatrics

Chairman: Dr. Craig D. Butler, 715 Lake St., Oak Park.
Secretary: Dr. A. J. Fletcher, 139 N. Vermilion, Danville.
Place: Springfield. Time: May 19-21, 1942.

Indiana State Pediatric Society

President: Dr. K. T. Knode, 1105 E. Jefferson Blvd., South Bend.
Secretary-Treasurer: Dr. Mathew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

Iowa Pediatric Society

President: Dr. Mark L. Floyd, Children's Hospital, Iowa City.
Secretary-Treasurer: Dr. James Dunn, Davenport Bank Bldg., Davenport.

Louisiana State Pediatric Society

President: Dr. Julian Graubarth, 3431 Prytania St., New Orleans.
Secretary-Treasurer: Dr. W. C. Rivenbark, 3503 Prytania St., New Orleans.

Medical Society of State of New York, Section on Pediatrics

Chairman: Dr. Norman L. Hawkins, 11 Public Sq., Watertown, N. Y.
Secretary: Dr. William J. Orr, 135 Linwood Ave., Buffalo.

Medical Society of the State of Pennsylvania, Pediatric Section

Chairman: Dr. John D. Sturgeon Jr., 22 N. Gallatin Ave., Uniontown.
Secretary: Dr. Elwood W. Stitzel, 403 Central Trust Bldg., Altoona, Pa.
Place: Pittsburgh. Time: Sept. 29-Oct. 2, 1942.

Michigan State Medical Society, Pediatric Section

Chairman: Dr. Harry Towsley, University of Michigan Hospital, Ann Arbor.
Secretary: Dr. Leon DeVel, 110 E. Fulton, Grand Rapids.

Mississippi State Pediatric Society

President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Pl., Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson.

Nebraska Pediatric Society

President: Dr. Andrew G. Dow, 314 Medical Arts Bldg., Omaha.
Secretary-Treasurer: Dr. John M. Thomas, 301 N. 49th St., Omaha.
Place: As announced by Committee. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

NEW HAMPSHIRE PEDIATRIC SOCIETY

President: Dr. MacLean J. Gill, 14 N. State St., Concord.
Secretary-Treasurer: Dr. Ursula G. Sanders, 46 Pleasant St., Concord.
Time: Twice yearly.

NORTH CAROLINA PEDIATRIC SOCIETY

President: Dr. Thomas M. Watson, Greenville.
Secretary: Dr. Frederick B. Haar, Greenville.

OKLAHOMA STATE PEDIATRIC SOCIETY

President: Dr. Ben H. Nicholson, 301 N. W. 12th St., Oklahoma City.
Secretary: Dr. Luvern Hays, 108 W. 6th St., Tulsa.
Place: Oklahoma Club. Time: 6:30 p. m., fourth Friday of each alternate month from September to May, inclusive.

SOUTH CAROLINA PEDIATRIC SOCIETY

President: Dr. R. B. Josey, 1517 Hampton Ave., Columbia.
Secretary-Treasurer: Dr. Wilson Ball, South Carolina State Health Dept., Columbia.

TENNESSEE STATE PEDIATRIC SOCIETY

President: Dr. Kinsey M. Buck, 1193 Madison Ave., Memphis.
Secretary: Dr. Gilbert Eblen, 611 W. Main Ave., Knoxville.

TEXAS PEDIATRIC SOCIETY

President: Dr. P. E. Luecke, 4105 Live Oak St., Dallas.
Secretary-Treasurer: Dr. John Ashby, 3610 Fairmount Ave., Dallas.

VIRGINIA PEDIATRIC SOCIETY

President: Dr. John M. Bishop, 511 Medical Arts Bldg., Roanoke.
Secretary: Dr. Edwin A. Harper, 301 Rivermont Ave., Lynchburg.

WEST VIRGINIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

President: Dr. Theresa O. Snaith, 450 Center Ave., Weston.
Secretary: Dr. Henrietta L. Marquis, 211 Bair Bldg., Beckley.

LOCAL

ACADEMY OF MEDICINE OF CLEVELAND, PEDIATRIC SECTION

Chairman: Dr. J. D. Nourse, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. I. B. Silber, 10465 Carnegie Ave., Cleveland.
Place: Cleveland Medical Library Bldg. Time: October, December, February and April.

ACADEMY OF MEDICINE, TORONTO, SECTION OF PEDIATRICS

President: Dr. I. Nelles Silverthorne, 170 St. George St., Toronto, Canada.
Secretary: Dr. G. P. Hamblin, 2333 Bloor St. W., Toronto, Canada.

BRONX PEDIATRIC SOCIETY

President: Dr. David Zahn, 2474 Valentine Ave., New York.
Secretary: Dr. Harry J. Cohen, 975 Walton Ave., New York.
Place: Concourse Plaza Hotel, 161st St. and Grand Concourse. Time: Every second Wednesday of each month, except June, July, August and September.

Brooklyn Academy of Pediatrics

President: Dr. Paul L. Parrish, 52 S. Oxford St., Brooklyn.
Secretary: Dr. Lewis A. Koch, 62 Pierrepont St., Brooklyn.
Place: Granada Hotel. Time: Fourth Wednesday of each month, except May, June, July, August and September.

Central New York Pediatric Club

President: Dr. Frank van der Bogert, 111 Union St., Schenectady.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Places: Various cities in New York. Time: Third Tuesday of April and September.

Chicago Pediatric Society

President: Dr. James H. Wallace, 715 Lake St., Oak Park, Ill.
Secretary: Dr. Henry G. Poncher, 1819 W. Polk St., Chicago.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May, inclusive.

Dallas Pediatric Society

President: Dr. Edgar Loomis, 351 W. Jefferson Ave., Dallas, Texas.
Secretary-Treasurer: Dr. John E. Ashby, 3610 Fairmont Ave., Dallas, Texas.
Place: Bradford Baby Hospital. Time: 1 p. m., second and fourth Saturdays of each month.

Detroit Pediatric Society

President: Dr. Marsh M. Poole, 773 Fisher Bldg., Detroit, Mich.
Secretary: Dr. Donald J. Barnes, 773 Fisher Bldg., Detroit, Mich.
Place: Wayne County Medical Society. Time: 8:30 p. m., first Wednesday of each month from October to June, inclusive.

•Fulton County Medical Society, Pediatrics Section (Atlanta, Ga.)

Chairman: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.
Secretary: Dr. Harry Lange, 478 Peachtree St. N. E., Atlanta.
Place: Academy of Medicine, 38 Prescott St. N. E. Time: Second Thursday of each month from October to April, 8 p. m.

Houston Pediatric Society

President: Dr. Raymond Cohen, 2300 Caroline St., Houston, Texas.
Secretary: Dr. Betty Moody, 526 Richmond Rd., Houston, Texas.
Place: College Inn, Houston. Time: Fourth Monday of each month.

Kansas City (Missouri) Pediatric Society

President: Dr. John Aull, 1103 Grand Ave., Kansas City.
Secretary: Dr. George Herrmann, 1107 Bryant Bldg., Kansas City.
Place: Kansas City General Hospital. Time: On call.

Los Angeles County Medical Association, Pediatric Section

President: Dr. Alonzo Cass, 1908 Wilshire Blvd., Los Angeles.
Secretary-Treasurer: Dr. Gladys Patric Shahovitch, 3936 Roderick Rd., Los Angeles.
Place: Los Angeles County Medical Headquarters, 1925 Wilshire Blvd. Time: Second Monday of February, April, June, October and December.

MEDICAL SOCIETY OF THE COUNTY OF KINGS AND THE ACADEMY OF MEDICINE OF BROOKLYN, PEDIATRIC SECTION

President: Dr. Sydney Nussbaum, 247 Ocean View Ave., Brooklyn.
Secretary: Dr. Harry S. Bikoff, 850 St. Marks Ave., Brooklyn.
Place: 1313 Bedford Ave., Brooklyn. Time: 9:00 p. m., fourth Monday of each month, October to April, inclusive.

MEDICAL SOCIETY OF THE COUNTY OF QUEENS, INC., SECTION ON PEDIATRICS

Chairman: Dr. A. A. Trivilino, 88-07–150th St., Jamaica, N. Y.
Secretary-Treasurer: Dr. Edith A. Mittell, 144–38th Ave., Flushing, N. Y.
Place: Queens County Medical Bldg., Forest Hills, N. Y. Time: Third Monday of October, January, March and May.

MEDICAL SOCIETY OF THE DISTRICT OF COLUMBIA, SECTION ON PEDIATRICS

President: Dr. Harry A. Ong, 1801 I St. N. W., Washington, D. C.
Secretary-Treasurer: Dr. William F. Burdick, 5402 Connecticut Ave. N. W., Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N. W. Time: 8 p. m., fourth Thursday of every month.

MEMPHIS PEDIATRIC SOCIETY

President: Dr. E. C. Mitchell, 1073 Madison Ave., Memphis, Tenn.
Secretary-Treasurer: Dr. Harry Jacobson, 1193 Madison Ave., Memphis, Tenn.
Place: John Gaston Hospital. Time: Quarterly.

MILWAUKEE PEDIATRIC SOCIETY

President: Dr. John H. Reynolds, 1628 W. Wisconsin Ave., Milwaukee.
Secretary-Treasurer: Dr. F. J. Mellencamp, 324 E. Wisconsin Ave., Milwaukee.
Place: Milwaukee Athletic Club. Time: Second Wednesday of each alternate month, beginning with February.

NEW YORK ACADEMY OF MEDICINE, SECTION OF PEDIATRICS

Chairman: Dr. Alfred Langmann, 108 E. 68th St., New York.
Secretary: Dr. Edith M. Lincoln, 600 Park Ave., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from October to May, inclusive, 8:30 p. m.

NORTHERN CALIFORNIA AFFILIATES

President: Dr. Crawford Bost, 490 Post St., San Francisco.
Secretary: Dr. William A. Reilly, 384 Post St., San Francisco.
Time: Second Thursday of September, November, January, March and May.

NORTHWESTERN PEDIATRIC SOCIETY

President: Dr. John M. Adams, 1009 Nicollet Ave., Minneapolis.
Secretary-Treasurer: Dr. Albert V. Stoesser, 205 W. University Hospital, Minneapolis.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

OKLAHOMA CITY PEDIATRIC SOCIETY

President: Dr. J. Byron Snow, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. G. R. Felts, 1200 N. Walker St., Oklahoma City.
Place: Oklahoma Club. Time: Fourth Friday of each alternate month.

Philadelphia Pediatric Society

President: Dr. Philip S. Barda, 222 W. Harvey St., Germantown, Pa.
Secretary: Dr. Aims C. McGuinness, Children's Hospital, 1740 Bainbridge St., Philadelphia.
Place: College of Physicians, 19 S. 22d St. Time: Second Tuesday of each month from October to April, inclusive.

Pittsburgh Pediatric Society

President: Dr. E. L. Piper, 3200–5th Ave., Pittsburgh.
Secretary-Treasurer: Dr. Carl Ruder, 646 Washington Rd., Mount Lebanon, Pittsburgh.
Place: Pittsburgh Academy of Medicine. Time: Second Friday, alternate month from October to June, inclusive.

Richmond Pediatric Society

President: Dr. Louise Fry Galvin, 214 S. Boulevard, Richmond, Va.
Secretary-Treasurer: Dr. Herman W. Farber, 501 E. Franklin St., Richmond, Va.
Place: Richmond Academy of Medicine, 1200 E. Clay St. Time: 8 p. m., third Thursday of each month, except June, July and August.

Rochester Pediatric Society

President: Dr. Herbert Soule, 122 Rutgers St., Rochester, N. Y.
Secretary-Treasurer: Dr. Jerome Glaser, 300 S. Goodman St., Rochester, N. Y.
Place: Rochester Academy of Medicine or arrangement by program committee. Time: Third Friday of each month from October to May.

St. Louis Pediatric Society

President: Dr. Maurice J. Lonsway, 3720 Washington Blvd., St. Louis.
Secretary-Treasurer: Dr. Mary A. McLoon, 408 Humboldt Bldg., St. Louis.
Place: St. Louis Medical Society Bldg. Time: First Friday of each month from October to June.

Seattle Pediatric Society

President: Dr. Frederick B. Jay, Stimson Bldg., Seattle.
Secretary: Dr. Sherod M. Billington, Medical Dental Bldg., Seattle.
Place: College Club. Time: Third Friday of each month from September to June at 6:30 p. m.

Southwestern Pediatric Society

President: Dr. Norman Nixon, 1136 W. 6th St., Los Angeles.
Secretary: Dr. Donald C. Shelby, 3780 Wilshire Blvd., Los Angeles.
Place: Jonathan Club of Los Angeles. Time: First Wednesday in January, March, May, September and November.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Campbell Harvey, 35 W. Huron St., Pontiac, Mich.
Secretary: Dr. Harry A. Towsley, University of Michigan, Department of Pediatrics and Communicable Diseases, Ann Arbor, Mich.
Time: Autumn, 1941.

Westchester County Medical Society, Pediatrics Section (New York)

President: Dr. John B. Ahouse, 27 Ludlow St., Yonkers, N. Y.
Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Rd., Rye.
Place: Grasslands Hospital, Valhalla, N. Y. Time: Third Thursday in October, December, February and April.